Alabama Medicaid Agency
Pharmacy and Therapeutics Committee
Pharmacotherapy Reviews

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review
HMG-CoA Reductase Inhibitors (AHFS Class 240608) Single Entity Agents
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I. Overview

Hydroxy-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (commonly referred to as "statins") work by inhibiting HMG-CoA reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate in an early step in the biosynthetic pathway for cholesterol. The inhibition of this enzyme decreases cholesterol synthesis causing an up-regulation of hepatic low-density lipoprotein (LDL) cholesterol receptors and enhanced clearance of circulating LDL cholesterol (LDL-C).

Lowering total cholesterol and LDL-C and raising high-density lipoprotein cholesterol (HDL-C) are important for many reasons. Deposition of cholesterol in the arterial walls is central to the pathogenesis of atherosclerosis in the coronary arteries. A direct correlation exists between total cholesterol, LDL-C, and the risk of developing coronary heart disease (CHD). Every 1% reduction in LDL-C results in a 1.7% decrease in the risk of a major coronary event.   An inverse relationship exists between HDL-C and the risk for developing CHD—every 1mg/dL decrease in HDL-C results in a 2-3% increase in the risk of CHD.[1] Thus, pharmacotherapy that can lower total cholesterol and LDL-C while raising HDL-C is worthwhile. Additionally, CHD statistics in the U.S. from 2002 indicated that 1.1 million adults experienced a new or recurrent myocardial infarction (MI) and 40% of those resulted in death. It is estimated that $100 billion is spent each year in the U.S. for direct and indirect costs associated with CHD.[2] Given that CHD is the leading cause of death in the U.S. for both men and women and that approximately 102 million Americans have total cholesterol levels greater than or equal to 200mg/dL (with 41 million American adults having levels of 240mg/dL or above), [3] it seems prudent to screen for and aggressively treat patients with hyperlipidemia.

HMG-CoA reductase inhibitors are considered first-line agents for treating hyperlipidemia due to their ability to lower total cholesterol and LDL-C. These agents also have the ability to moderately raise HDL-C. Table 1 lists the statins included in this review. This review encompasses all dosage forms and strengths.

Table 1. HMG-CoA Reductase Inhibitors in this Review

Generic Name	Example Brand Name(s)
Atorvastatin	Lipitor
Fluvastatin	Lescol
	Lescol XL
Lovastatin	Mevacor*
	Altocor
Pravastatin	Pravachol
Simvastatin	Zocor

* Generic available in at least one dosage form or strength

Rosuvastatin (Crestor) was FDA approved in August 2003. Per Alabama Medicaid P & T policy, rosuvastatin is eligible for review after it has been commercially available for at least 6 months. Rosuvastatin will therefore be reviewed at a future time.

II.   Current Treatment Guidelines

The decision to treat hyperlipidemia generally follows the treatment guidelines of the Third Report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III.[4]   Because LDL-C is the major atherogenic lipid component, NCEP-ATP III focuses primarily on attaining goal LDL-C levels.

Goal levels of LDL-C vary depending on CHD risk factors present. In brief, the major risk factors for CHD, which are used to modify LDL-C goal, are listed in the following table.

Table 2. Major Risk Factors that Modify LDL-C Goal[4]

Positive Risk Factors (increase the risk for CHD)	Negative Risk Factors* (decrease the risk for CHD)
• Age (men $\geq$ 45 years; women $\geq$ 55 years) • Family history of premature CHD (first degree male relative < 55 years; first degree female relative < 65 years) • Current cigarette smoking • Hypertension (BP $\geq$ 140/90 or the use of antihypertensives) • Low HDL-C (< 40 mg/dL)	• High HDL-C ($\geq$ 60 mg/dL)

*Presence of a negative risk factor removes one positive risk factor from the total count of risk factors.

Diabetes, clinical CHD, symptomatic carotid artery disease, peripheral arterial disease, and aortic abdominal aneurysm are considered CHD risk equivalents. Once a patient's risk factors are assessed, it is appropriate to calculate 10-year CHD risk in patients with 2 or more risk factors (other than LDL-C) who do not have clinically manifested CHD or a CHD risk equivalent. Calculating this short-term risk helps identify individuals who may benefit from more intensive treatment. This risk is tabulated based on the patient's age, total cholesterol, HDL-C, systolic blood pressure, and smoking status.   Risk is then assigned to one of three categories describing the risk of developing CHD or experiencing a coronary event in the next 10 years:
- High risk = > 20% CHD risk
- Intermediate risk = 10-20% CHD risk
- Low risk = < 10% CHD risk

Once CHD risk is determined, the goal LDL-C is determined. The following table details goal levels of LDL-C along with when to initiate therapeutic lifestyle changes (TLC) and when to initiate pharmacotherapy.

Table 3. LDL-C Categories and Cut-points for TLC and Drug Therapy Per Risk Category[4]

Risk Category	LDL-C Goal	LDL-C Level at Which to Initiate Therapeutic Lifestyle Changes	LDL-C Level at Which to Consider Drug Therapy
CHD or CHD Risk Equivalent (10-year risk > 20%)	< 100 mg/dL	$\geq$ 100 mg/dL	$\geq$ 130 mg/dL (100-129 mg/dL, drug optional)*
2+ Risk Factors (10-year risk $\leq$ 20%)	< 130 mg/dL	$\geq$ 130 mg/dL	$\geq$ 130 mg/dL (for 10-year risk 10-20%) > 160 mg/dL (for 10-year risk < 10%)
0-1 Risk Factor	< 160 mg/dL	$\geq$ 160 mg/dL	$\geq$ 190 mg/dL (160-189 mg/dL, drug optional)**

*Some authorities recommend use of LDL-C lowering drugs in this category if an LDL-C < 100 mg/dL cannot be achieved by TLC. Clinical judgment also may call for deferring drug therapy in this category.
**Factors that favor drug therapy after 3 months of TLC include a severe single risk factor (heavy cigarette smoking, poorly controlled hypertension, strong family history or premature CHD, or very low HDL-C), multiple life-habit risk factors and emerging risk factors, or 10-year risk approaching 10%.

III. Comparative Indications for HMG-CoA Reductase Inhibitors

The Food and Drug Administration (FDA) approved all HMG-CoA reductase inhibitors for use in adjunct to diet for the reduction of total cholesterol and LDL-C in patients with primary hypercholesterolemia. Table 4 summarizes the FDA-approved indications for each of the statins in this review.

Table 4. FDA-Approved Indications for the HMG-CoA Reductase Inhibitors[5-10]

Indication	Atorvastatin	Fluvastatin/ Fluvastatin XL	Lovastatin	Lovastatin ER	Pravastatin	Simvastatin
Primary Prevention of Cardiovascular Events			✔	✔	✔	✔ *
Secondary Prevention of Cardiovascular Events		✔ **			✔	✔ *
Primary Hypercholesterolemia/ Mixed Dyslipidemia	✔	✔	✔	✔	✔	✔
Homozygous Familial Hyperlipidemia	✔					✔
Primary Dysbetalipoproteinemia	✔				✔	✔
Regression of coronary atherosclerosis		✔	✔	✔	✔	
Heterozygous Familial Hypercholesterolemia in adolescents	✔		✔		✔	✔
Hypertriglyceridemia	✔				✔	✔

*Approved for patients as high-risk of coronary events because of existing CHD, diabetes, peripheral vascular disease, history of stroke or other cerebrovascular disease to reduce mortality by reducing CHD deaths, to reduce the risk of non-fatal MI and stroke, and to reduce the need for coronary and non-coronary revascularization procedures.

** To reduce risk of undergoing coronary revascularization procedures in patients with CHD

IV.   Comparative Pharmacokinetic Parameters of HMG-CoA Reductase Inhibitors

Minor differences exist between the statins in regard to pharmacokinetic parameters. Of main concern is the metabolizing enzymes, which result in clinically significant drug interactions for the drugs in this class. All statins possess low systemic bioavailability indicating extensive first pass metabolism, which is advantageous since the major site of cholesterol synthesis is in the liver. Table 5 summarizes various pharmacokinetic parameters of the statins.

Table 5. Pharmacokinetic Parameters of HMG-CoA Reductase Inhibitors[5-10]

Parameter	Atorvastatin	Fluvastatin/ Fluvastatin XL	Lovastatin	Lovastatin ER	Pravastatin	Simvastatin
Systemic Bioavailability	30%	24-29%	< 5%	190% compared to lovastatin	17%	< 5%
Protein Binding	$\geq$ 98%	98%	> 95%	> 95%	50%	95%
Lipid Solubility	Hydrophilic	Hydrophilic	Lipophilic	Lipophilic	Hydrophilic	Lipophilic
Crosses Blood-brain Barrier	No	No	Yes	Yes	No	Yes
Main Metabolizing Enzyme	CYP3A4	CYP2C9	CYP3A4	CYP3A4	None	CYP3A4

V.   HMG-CoA Reductase Inhibitor Drug Interactions

Clinically important drug interactions exist for the statins with minor differences between the drugs in this class when thinking about their use in the general population. Since atorvastatin, lovastatin, and simvastatin are metabolized via CYP34A, they share similar drug interactions. Fluvastatin is metabolized via CYP2C9 whereas pravastatin is not appreciably metabolized by the CYP system. Specific drug interaction studies have not been performed with lovastatin ER; however, the drug interactions listed in the package insert for lovastatin ER are similar to that of non extended-release lovastatin.

Each statin should be used cautiously when combined with bile acid sequestrants (due to potential for decreased pharmacological effects of the statin), niacin and fibric acid derivatives such as gemfibrozil (due to increased risk for myopathy and rhabdomyolysis), and azole antifungals (due to increased plasma levels of the statin which could lead to increased side effects and increased risk for rhabdomyolysis). Each statin, with the exception of fluvastatin/fluvastatin XL, should also be used cautiously with cyclosporine (due to increased plasma levels of the statin which could increase risk for side effects including myolysis and rhabdomyolysis). Dosage reduction of the statin and monitoring for side effects is warranted to properly manage this interaction.[11,12]

Other clinically significant [rated as 1 (major) or 2 (moderate)] drug interactions for the statins are listed below. [11,12]

Atorvastatin, Lovastatin, Simvastatin
- Grapefruit juice (> 1 quart/day can increase risk of myopathy; management: drink < 1 quart/day)[10]
- Macrolide Antibiotics (increase in plasma levels of statins increasing risk for myopathy; management: suspend statin until antibiotic complete)
- Nefazodone (increased risk for myopathy and rhabdomyolysis; management: monitor patients more closely for side effects or avoid statin therapy unless benefits outweigh the risks)
- Non-dihydropyridine CCBs (increased plasma concentration of the statin; management: reduce statin dose)
- Protease Inhibitors (atorvastatin & simvastatin only— increased risk for myopathy and rhabdomyolysis; management: monitor patients more closely for side effects or avoid statin therapy unless benefits outweigh the risks)
- Rifamycins (effects of statin reduced; management: monitor for effectiveness and increase statin dose if needed)
- Warfarin (lovastatin only—anticoagulant effect may increase; management: monitor and adjust warfarin dose if needed)

Fluvastatin/Fluvastatin XL
- Rifamycins (effects of statin reduced; management: monitor for effectiveness and increase statin dose if needed)
- Warfarin (anticoagulant effect may increase; management: monitor and adjust warfarin dose if needed)

Pravastatin
- Protease Inhibitors (decreased effectiveness of pravastatin; management: monitor for a decreased effect)

Most of the drug interactions listed above can be managed with appropriate dosing modifications and monitoring. Atorvastatin, lovastatin, and simvastatin should not be used concomitantly with nefazodone and protease inhibitors unless benefits of therapy outweigh the risks for potential side effects. However, nefazodone and protease inhibitors are used in specific patient populations and not the general population for which we are evaluating the use of statins. When considering the general population, use of any statin would not be precluded due to potentially harmful drug interactions. Of note, to avoid potential harm, the package insert for simvastatin offers one advantage in that it explicitly details instructions for proper use and dosing of simvastatin when used concomitantly with interacting drugs.

VI.   Comparative Adverse Effects of HMG-CoA Reductase Inhibitors

Statins are generally well tolerated with the most common side effects being minor abdominal pain, constipation, gas/flatulence, and headache. More serious but rare side effects of statins include increases in liver enzymes and myopathy accompanied by elevations in creatine kinase, which can progress to rhabdomyolosis and acute renal failure. Routine liver function monitoring is recommended with each statin with only slight variations in this monitoring parameter existing between statins. [5-10] Increases in hepatic transaminases (> 3x ULN) have been reported with each statin (0.5%-2.0%) and appear to be dose-dependent (risk increases as the statin dose increases). [13,14] Elevations in hepatic transaminases frequently reverse with a reduction in dose or suspension of therapy. And, upon re-challenge or initiation of another statin, elevations in liver enzymes do not often occur. [14] Myositis (defined as elevated creatine kinase— generally > 10 times the ULN—plus muscle aches/weakness) has also been reported with each statin (0.1-0.5%), as has rhabdomyolysis when statins are used as monotherapy (0.04-0.2%). [15] However, no clear differences exist between the statins in the rates of these rare but serious adverse reactions. [14]

Additionally, in regard to more minor adverse reactions, no clear differences seem to exist between the drugs in this class. Patients that do not tolerate one statin generally may tolerate another (tolerability differences between statins exist for unknown reasons). Table 6 lists adverse reactions reported with the various statins. Incidences of adverse effects are listed as percentages with the placebo incidence listed in parentheses.

Table 6. Adverse Reactions (%) Reported with the HMG-CoA Reductase Inhibitors [5-10]

Adverse Effects	Atorvastatin	Fluvastatin/ Fluvastatin XL	Lovastatin	Lovastatin ER	Pravastatin	Simvastatin
Abdominal Pain	0 - 3.8 (0.7)	2.1 – 3.8 (2.0) / 3.7 (3.8)	2.0 – 2.5 (1.6)	N/A[#]	5.4 (6.9)	3.2 (3.2)
Asthenia	0 – 3.8 (1.9)	N/A[#] / N/A[#]	1.2 – 1.7 (1.4)	3.0 (6.0)	N/A[#]	1.6 (2.5)
Constipation	0 – 2.5 (1.8)	1.8 – 2.8 (2.5) / 2.3 (3.3)	2.0 – 3.5 (1.9)	N/A[#]	4.0 (7.1)	2.3 (1.3)
Diarrhea	0 – 5.3 (1.5)	1.5 – 2.5 (2.1) / 3.3 (4.2)	2.2 – 2.6 (2.3)	3.0 (6.0)	6.2 (5.6)	1.9 (2.5)
Dizziness	$\geq$ 2*	0.5 – 1.1 (1.8) / 1.9 (2.5)	0.5 – 1.2 (0.7)	2.0 (6.0)	3.3 (3.2)	N/A[#]
Dyspepsia	1.3 – 2.8 (4.1)	4.7 – 7.3 (2.3) / 3.5 (3.2)	1.0 – 1.6 (1.9)	N/A[#]	N/A[#]	1.1 (N/A)[#]
Flatulence	1.1 – 2.8 (3.3)	1.6 – 2.5 (2.2) / 1.4 (2.5)	3.7 -4.5 (4.2)	N/A[#]	2.7 (3.4)	1.9 (1.3)
Headache	2.5 – 16.7 (7.0)	1.9 – 3.8 (3.0) / 4.7 (7.8)	2.1 – 3.2 (2.7)	7.0 (6.0)	6.2 (3.9)	3.5 (5.1)
Myalgia	0 – 5.6 (1.1)	1.7 – 2.7 (2.3) / 3.8 (4.5)	1.8 – 3.0 (1.7)	3.0 (15.0)	2.7 (1.0)	1.2 (1.3)
Nausea	$\geq$ 2*	0.8 – 2.0 (1.4) / 2.5 (2.0)	1.9 – 2.5 (2.5)	N/A[#]	7.3 (7.1)	1.3 (1.9)

* Placebo incidence not provided
\# Incidence not available

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VII. Dosing and Administration of HMG-CoA Reductase Inhibitors

All statins are dosed once daily with the exception of maximum doses of lovastatin and fluvastatin non extended-release products, which should be divided into twice daily dosing. Minor differences in administration exist between the statins but none of these are clinically relevant enough to provide advantages of one statin over another. Table 7 below details dosing and administration guidelines for the drugs in this class.

Table 7. HMG-CoA Reductase Inhibitor Dosing & Administration[5-10]

	Atorvastatin	Fluvastatin/ Fluvastatin XL	Lovastatin	Lovastatin ER	Pravastatin	Simvastatin
Initial Dose	10-20mg QD	20-80mg QD	20mg QD	20-60mg QD	40mg QD	20-40mg QD
Dosing Range	10-80mg QD	20-80mg* QD	10-80mg[#] QD	10-60mg QD	10-80mg QD	5-80mg QD
Maximum Dose	80mg QD	80mg QD	80mg QD	60mg QD	80mg QD	80mg QD
Administration	Can be taken anytime of the day with or without food	Should be taken at bedtime	Should be taken with evening meal (morning & evening if BID)	Should be taken at bedtime	Should be taken on an empty stomach or at bedtime	Should be taken in the evening
Special Considerations for initiating therapy	LDL-C reduction $\geq$ 45%, initiate at 40mg QD	LDL-C reduction < 25%, initiate at 20mg QD; LDL-C reduction > 25%, initiated based on needed reduction	LDL-C < 20%, initiate at 10mg/day	LDL-C < 20%, initiate at 10mg/day	Initiate at 10mg/day in patients with significant renal or hepatic dysfunction	LDL-C reduction $\geq$ 45% or is deemed at high risk for a CHD event, initiate at 40mg QD

* 80mg dose should be given as 40mg BID if non-extended release formulation used
# 80mg dose should be given as 40mg BID

VIII. Comparative Effectiveness of the HMG-CoA Reductase Inhibitors

Two main factors are typically considered when assessing efficacy of statins: 1) the capacity to reduce lipids, especially LDL-C since this cholesterol component has been identified as a major risk factor for CHD and is the target of NCEP-ATP III guidelines; and 2) outcomes data, specifically morbidity parameters (including primary and secondary prevention) and mortality. HMG-CoA Reductase Inhibitors reduce total cholesterol, LDL-C, and triglycerides while raising HDL-C in a dose-dependent manner.[5-10] Differences do exist however, between the statins and their cholesterol-lowering capacity (including LDL-C lowering capacity). Table 8 below compares the cholesterol-lowering effects of each statin.

Table 8. HMG-CoA Reductase Inhibitors' Effects on Cholesterol Levels[5-10]

Statin	Daily Dosage Range	Effect On:			
		TC	LDL-C	TG	HDL-C
Atorvastatin	10mg – 80mg	↓ 29-45%	↓ 39-60%	↓ 19-37%	↑ 5-9%
Fluvastatin/ Fluvastatin XL	20mg – 80mg	↓ 17-27% / ↓ 25%	↓ 22-36% / ↓ 35%	↓ 12-23% / ↓ 19%	↑ 3-9% / ↑ 7%
Lovastatin	10mg – 80mg	↓ 16-34%	↓ 21-42%	↓ 6-27%	↑ 2-9%
Lovastatin ER	10mg – 60mg	↓ 18-29%	↓ 24-41%	↓ 10-25%	↑ 9-13%
Pravastatin	10mg – 80mg	↓ 16-27%	↓ 22-37%	↓ 11-24%	↑ 2-12%
Simvastatin	5mg – 80mg	↓ 19-36%	↓ 26-47%	↓ 12-33%	↑ 8-16%

TC = Total Cholesterol   LDL-C = Low-density Lipoprotein Cholesterol   TG = Triglycerides   HDL-C = High-density Lipoprotein Cholesterol

Since LDL-C reduction is the focus of the NCEP-ATP III[4] treatment guidelines, Table 9 below provides a dose-based comparison of the statins and their ability to lower LDL-C.

Table 9. HMG-CoA Reductase Inhibitor Dose Related LDL-C Reductions[5-10]

Statin	Dose	LDL-C Reduction
Atorvastatin	10mg/day	39%
	20mg/day	43%
	40mg/day	50%
	80mg/day	60%
Fluvastatin/ Fluvastatin XL	20mg/day	22%
	40mg/day	25%
	80mg/day	35-36%
Lovastatin	10mg/day	21%
	20mg/day	27%
	40mg/day	31%
	80mg/day*	42%
Lovastatin ER	10mg/day	24%
	20mg/day	30%
	40mg/day	36%
	60mg/day	41%
Pravastatin	10mg/day	22%
	20mg/day	32%
	40mg/day	34%
	80mg/day	37%
Simvastatin	5mg/day	26%
	10mg/day	30%
	20mg/day	38%
	40mg/day	41%
	80mg/day	47%

* Dosed as 40mg BID

Randomized controlled trials (RCTs) that measured patient-oriented outcomes (morbidity parameters and mortality) exist for each of the statins, with the exception of fluvastatin XL and lovastatin ER. Major RCTs that measured patient-oriented outcomes are summarized on the following pages for each drug in this class.

Table 10. Evidence for Atorvastatin[#]

Study	Sample	Duration	Results
AVERT[16]	n = 341 mean age 59 years with stable coronary disease and a baseline LDL-C ≥ 115 mg/dL	1.5 years	Compared to revascularization procedure, atorvastatin 80mg/day resulted in: • 13% of patients receiving atorvastatin compared to 21% of patients receiving revascularization experienced an ischemic event (p = 0.048)
MIRACL[17]	n = 3,086 age > 18 years (mean 65 years) with unstable angina or non-Q-wave acute MI (atorvastatin given within 24-96 hrs after the acute coronary syndrome)	16 weeks	Compared to placebo, atorvastatin 80mg/day resulted in: • 16% (95%CI 1-30) ↓ risk of a composite of death, nonfatal acute MI, resuscitated cardiac arrest, & recurrent symptomatic myocardial ischemia requiring hospitalization (placebo =17.4%, tx =14.8%; p = 0.048)* • no statistically significant differences were found in the individual components of the above primary outcome with the exception of recurrent ischemia requiring hospitalization (26%, 95%CI 5-43 ↓ risk; p = 0.02) • 50% (95%CI 1-74) ↓ risk of fatal and nonfatal stroke (placebo = 1.6%, tx = 0.8%; p = 0.045)
GREACE[18]	n = 1,600 age < 75 years (mean 58 years) with established CHD and a baseline LDL-C > 100mg/dL (secondary prevention)	3 years	Compared to placebo (termed 'usual care'), atorvastatin 10-80mg/day (mean dose 24mg/day) resulted in: • 51% (95%CI 27-73) ↓ risk in CHD recurrent event or death (placebo =24.5%, tx =12%; p < 0.0001)* • 43% (95%CI 22-61) ↓ risk in total mortality (placebo =5%, tx =2.9%; p = 0.0021)* • 47% (95%CI 18-70) ↓ risk of stroke (placebo = 2.1%, tx = 1.1%; p = 0.034)* • 47% (95%CI 26-71) ↓ risk of coronary mortality (placebo =4.8%, tx =2.5%; p = 0.0017) • 54% (95%CI 29-75) ↓ risk of coronary morbidity (p < 0.0001)
ASCOT-LLA[19]	n = 10,305 age 40-79 years (mean 63 years) with a baseline TC ≤ 251mg/dL and at least 3 risk factors for CHD (primary prevention)	3.3 years	Compared to placebo, atorvastatin 10mg/day resulted in: • 36% (95%CI 17-50) ↓ risk of a composite nonfatal MI and fatal CHD (placebo = 3.0%, tx = 1.9%; p = 0.0005)* • 21% (95%CI 10-31) ↓ risk in total CV events & procedures (placebo = 9.5%, tx = 7.5%; p = 0.0005) • 29% (95%CI 14-41) ↓ risk for total coronary events (placebo = 4.8%%, tx = 3.4%; p = 0.0005) • 13% (95%CI –6–29) nonsignificant ↓ risk in all cause mortality (placebo = 4.1%, tx = 3.6%; p = 0.1649) • 27% (95%CI 4-44) ↓ risk of fatal or nonfatal stroke (placebo = 2.4%, tx = 1.7%; p = 0.0236)

ASAP[20] and ARBITER[21] trials were not included due to lack of patient-oriented outcomes in these trials (studies primarily focused on the disease-oriented outcome of carotid intima medial thickness). CARDS[22] trial will not be completed until early 2005 (expected date per study investigators) and thus is also not included in this review. The Bertolini et al. study[23] was not included in this review due to lack of patient-oriented outcomes (study primarily designed to compare cholesterol lowering capacity and side effects between atorvastatin and pravastatin). The CURVES study[24] was not included in this review due to lack of patient-oriented outcomes (study primarily designed to compare dose efficacy of atorvastatin to simvastatin, pravastatin, lovastatin, and fluvastatin).

* Primary outcome of the study

Table 11. Evidence for Fluvastatin

Study	Sample	Duration	Results
LIPS[25]	n = 1,677 age 18-80 years with stable or unstable angina following successful completion of percutaneous coronary intervention (PCI) and a baseline TC of 133-270 mg/dL	3.9 years	Compared to placebo, fluvastatin 40mg BID resulted in: • 22% (95%CI 5-36) ↓ risk of a composite of cardiac death, nonfatal MI, or reintervention procedure (placebo =26.7%, tx =21.4%; p = 0.01)* • Nonsignificant trends towards ↓ cardiac death (p = 0.07), and combined cardiac death + nonfatal MI (p = 0.07)

* Primary outcome of the study

Table 12. Evidence for Lovastatin#

Study	Sample	Duration	Results
ACAPS[26]	n = 919 age 40-79 years with early carotid atherosclerosis (asymptomatic) and moderately elevated LDL-C	2.8 years	Compared to placebo, lovastatin 20-40mg/day resulted in: • ↓ risk in total mortality (placebo =8, tx =1; p =0.02) • ↓ risk for major CV events (placebo =14, tx =5; p = 0.04)
AFCAPS/TexCAPS[27]	n = 6,605 age 45-73 years and average TC, LDL-C and below average HDL-C without clinically evident atherosclerotic cardiovascular disease (primary prevention)	5.2 years	Compared to placebo, lovastatin 20-40mg/day resulted in: • 37% (95%CI 21-50) ↓ in risk for first acute major coronary event (placebo =183, tx =116; p < 0.001)* • 40% (95%CI 17-57) ↓ in risk of fatal or nonfatal MI (placebo =95, tx =57; p = 0.002) • 33% (95%CI 15- 48) ↓ in risk coronary revascularization procedures (placebo =157, tx =106; p = 0.001) • 32% (95%CI 5-51) ↓ in risk of unstable angina (placebo =87, tx =60; p = 0.02) • 25% (95%CI 9-38) ↓ in risk of CV events (placebo =255, tx =194; p =0.003) • 25% (95%CI 8-39) ↓ risk for coronary events (placebo =215, tx =163; p =0.006)

EXCEL[28] trial not included due to lack of patient-oriented outcomes studied in this trial (study primarily designed to measure cholesterol lowering and safety)
* Primary outcome of the study

Table 13. Evidence for Pravastatin

Study	Sample	Duration	Results
PMS-CRP[29]	n =1,062 age 20-86 years (mean 55 years) with baseline TC between 200-300 mg/dL plus 2 additional risk factors for CHD (primary prevention)	26 weeks	Compared to placebo, pravastatin 20-40mg/day resulted in: • Serious CV events (MI, unstable angina, acute CHF, sudden cardiac death) occurred less in the pravastatin group (placebo =13, tx =1; p < 0.001)
WOSCOPS[30]	n = 6,595 men aged 45-64 years with a baseline LDL-C of 175-209 mg/dL and no history of MI (primary prevention)	4.9 years	Compared to placebo, pravastatin 40mg/day resulted in: • 31% (95%CI 17-43) ↓ in risk for nonfatal MI or death from CHD (placebo = 248, tx =174; p = 0.001)* • 31% (95%CI 15-45) ↓ in risk of definite nonfatal MI (placebo =204, tx =143; p < 0.001) • 28% (95%CI –10-52) nonsignificant ↓ in death from definite CHD (placebo =52, tx =38; p = 0.13) • 33% (95%CI 1-55) ↓ in death from definite + suspected CHD (placebo =61, tx =41; p= 0.042) • 32% (95%CI 3-53) ↓ in death from all CV causes (placebo =73, tx =50; p = 0.033) • 22% (95%CI 0-40) nonsignificant ↓ in all cause mortality (placebo =135, tx =106; p = 0.051)
PLAC-II[31]	n = 151 coronary patients with moderately elevated LDL-C	3 years	Compared to placebo, pravastatin resulted in: • 60% nonsignificant reduction of nonfatal MI plus death caused by coronary artery disease (p = 0.09) • 61% reduction of any fatal events plus any nonfatal MI (p = 0.04) • 80% reduction of fatal plus any nonfatal MI (p = 0.03)
CARE[32]	n = 4,159 age 21-75 years with a previous MI and a baseline TC of < 240 mg/dL and LDL-C of 115-174 mg/dL (secondary prevention)	5 years	Compared to placebo, pravastatin 40mg/day resulted in: • 24% (95%CI 9-36) ↓ risk of death from CHD or nonfatal MI (placebo =13.2%, tx =10.2%; p = 0.003)* • 20% (95%CI -5-39) nonsignificant ↓ risk of death from CHD (placebo =5.7%, tx =4.6%; p =0.10) • 23% (95%CI 4-39) ↓ risk of nonfatal MI (placebo =8.3%, tx =6.5%; p = 0.02) • 37% (95%CI -5-62) nonsignificant ↓ risk of fatal MI (placebo =1.8%, tx =1.2%; p= 0.07) • 31% (95%CI 3-52) ↓ risk of stroke (placebo =3.8%, tx =2.6%; p =0.03)

* Primary outcome of the study

Table 13. Evidence for Pravastatin (con't) [#]

Study	Sample	Duration	Results
LIPID[33]	n = 9,014 age 31-75 years with a history of MI or unstable angina and a baseline TC of 155-271 mg/dL (secondary prevention)	6.1 years	Compared to placebo, pravastatin 40mg/day resulted in: • 24% (95%CI 12-35) ↓ risk of death due to CHD (placebo =8.3%, tx =6.4%; p < 0.001)* • 25% (95%CI 13-35) ↓ risk of death due to CV disease (placebo =9.6%, tx =7.3%; p < 0.001) • 22% (95%CI 13-31) ↓ risk of death from any cause (placebo =14.1%, tx =11%; p < 0.001) • 24% (95%CI 15-32) ↓ risk of death due to CHD or nonfatal MI (placebo =15.9%, tx =12.3%; p < 0.001) • 29% (95%CI 18-38) ↓ risk for any MI (placebo =10.3%, tx = 7.4%; p < 0.001) • 19% (95%CI 0-34) ↓ risk for any stroke (placebo 4.5%, tx =3.7%; p = 0.048)
PROSPER[34]	n = 5,804 age 70-82 years (mean 75 years) with a history of or risk factors for vascular (coronary, cerebral, or peripheral) disease and a baseline TC of 154-347 mg/dL	3.2 years	Compared to placebo, pravastatin 40mg/day resulted in: • 15% (95%CI 3-26) ↓ risk for the combined endpoint of death from CHD, nonfatal MI, and fatal or nonfatal stroke (placebo =16.2%, tx =14.1%; p = 0.014)* • 19% (95%CI 6-31) ↓ risk for CHD or nonfatal MI (placebo =12.2%, tx = 10.1%; p = 0.006) • 24% (95%CI 1-42) ↓ risk for CHD death (placebo = 4.2%, tx = 3.3%; p = 0.043) • no reduction was found for incidence of fatal or nonfatal stroke (p = 0.81) • nonsignificant differences in all-cause death (placebo = 10.5%, tx = 10.3%; p = 0.74)
ALLHAT-LLT[35]	n = 10, 355 age > 55 years (mean 66 years) and hypertensive with at least 1 additional risk factor for CHD and a baseline LDL-C of 120-189 mg/dL	4.8 years	Compared to 'usual care,' pravastatin 40mg/day resulted in: • no statistically significant difference was found between groups in all-cause mortality (RR 0.99, 95%CI 0.89-1.11; p = 0.88)* • no statistically significant difference was found between groups in CV disease deaths (RR 0.99, 95%CI 0.84-1.16; p = 0.91) • no statistically significant difference was found between groups in fatal or nonfatal strokes (RR 0.91, 95%CI 0.75-1.09; p = 0.31)

PLAC-I trial[36] was not included in this review due to lack of patient-oriented outcomes (the trial was primarily designed to measure changes in minimum lumen diameter to predict progression of CAD). KAPS trial[37] was not included in this review due to lack of patient-oriented outcomes (the trial was primarily designed to measure maximum carotid IMT; researchers reported clinical cardiovascular events to be lower in the pravastatin group although the difference was not statistically significant). REGRESS trial[38] was not included in this review due to lack of specific patient-oriented outcomes reporting (this trial was primarily designed to detect differences in angiographic restenosis as measured by diameter stenosis in patients post- PTCA; researchers also reported a 58% relative risk reduction in clinical endpoints with pravastatin compared to placebo with most of these events consisting of additional PTCA procedures. Incidence of MI, stroke and death not reported in the trial).

* Primary outcome of the study

Table 14. Evidence for Simvastatin

Study	Sample	Duration	Results
4S[39]	n =4,444 age 35-70 years with a history of angina or MI; baseline TC = 270 mg/dL (secondary prevention)	5.4 years	Compared to placebo, simvastatin 20-40mg/day resulted in: • 30% (95%CI 15-42) ↓ risk in total mortality (placebo =11.5%, tx =8.2%; p= 0.0003)* • 42% (95%CI 27-54) ↓ risk for coronary death (placebo =8.5%, tx =5.0%; p value not provided in study) • 34% (95%CI 25-41) ↓ risk for a major coronary event (placebo =28%, tx =19%; p < 0.00001) • 37% ↓ risk for myocardial revascularization procedure (placebo =17.2%, tx =11.3%; p < 0.00001)

* Primary outcome of the study

Table 14. Evidence for Simvastatin (con't)

Study	Sample	Duration	Results
HPS[40,41]	n = 20,536 (including 5,963 with diabetes) age 40-80 years considered to be at high risk for experiencing a major coronary event due to existing CHD, history of stroke or other CV disease, PVD, diabetes, or HTN in males > 65 years of age (primary and secondary prevention)	5 years	In the overall study sample, compared to placebo, simvastatin 40mg/day resulted in: • 13% (95%CI 6-19) ↓ risk in all-cause mortality (placebo =14.7%, tx = 12.9%; p = 0.0003)* • 17% (95%CI 9-25) ↓ risk for death from any vascular causes (placebo = 9.1%, tx = 7.6%; p < 0.0001) • 27% (95%CI 21-33) ↓ in first nonfatal MI or coronary death (placebo = 11.8%, tx =8.7%; p < 0.0001) • 24% (95%CI 19-28) ↓ in composite major coronary events, strokes, and revascularizations (placebo = 25.2%, tx =19.8%; p < 0.0001) • 25% (95%CI 15-34) ↓ in first nonfatal or fatal stroke (placebo =5.7%, tx =4.3%; p < 0.0001) • 24% (95%CI 17-30) ↓ in first revascularization procedure (placebo =11.7%, tx =9.1%; p < 0.0001) • In 6,793 patients with baseline LDL-C < 116mg/dL, major vascular events risk was decreased with simvastatin (placebo = 22.2%, tx = 17.6%; p < 0.0001) • In 3,421 patients with baseline LDL-C < 100mg/dL, major vascular events risk was decreased with simvastatin (placebo = 21%, tx = 16.4%; p = 0.0006) In subjects with diabetes, simvastatin 40mg/day resulted in: • 27% (95%CI 15-38) ↓ in first nonfatal MI or coronary death (placebo =12.6%, tx =9.4%; p < 0.0001) • 22% (95%CI 13-30) ↓ in composite major coronary events, strokes, and revascularizations (placebo = 25.1%, tx = 20.2%; p < 0.0001) • 24% (95%CI 6-39) ↓ in first nonfatal or fatal stroke (placebo =6.5%, tx =5.0%; p = 0.01) • 17% (95% CI 3-30) ↓ in first revascularization procedure (placebo =10.4%, tx =8.7%; p = 0.02) • 27% (95%CI 13-40) ↓ risk in major vascular events in the 2,426 diabetic patients with baseline LDL-C < 116mg/dL (placebo = 20.9%, tx = 15.7%; p < 0.0007)

* Primary outcome of the study

IX.   Conclusions

Lowering cholesterol (including LDL-C) reduces cardiovascular risk. Because LDL-C is the major atherogenic lipid component, NCEP-ATP III[4] focuses primarily on attaining goal LDL-C levels. All HMG-CoA Reductase Inhibitors have been shown to be safe (comparably) and effective for lowering cholesterol (including LDL-C); however, differences do exist between the statins and their capacity to lower total cholesterol and LDL-C.   All statins exert a dose dependent cholesterol lowering capacity (the higher the dose, the higher the capacity for cholesterol lowering). Furthermore, all drugs in this class with the exception of fluvastatin XL and lovastatin ER, are supported by patient-oriented evidence from randomized controlled trials, although the amount and strength of evidence differs between the statins.

Three main issues need to be considered when selecting a statin for preferred drug status:
   1)   Safety
   2)   Patient outcomes data
   3)   LDL-C lowering capacity

Safety
As previously discussed in section VI of this document, no clear differences seem to exist among the drugs in this class with regard to incidence of both minor and more serious adverse reactions. Patients that do not tolerate one statin generally may tolerate another. However, one point to consider is that risk for side effects increases with higher doses of statins. According to package insert information on each drug, lower doses of atorvastatin (10-20mg/day) provide greater LDL-C lowering capacity than maximum doses of fluvastatin/fluvastatin XL, lovastatin and lovastatin ER, and pravastatin.   Lower doses of simvastatin ($\leq$ 20mg/day) provide greater LDL-C reduction than lower doses ($\leq$ 20mg/day) of fluvastatin/fluvastatin XL, lovastatin and lovastatin ER, and pravastatin.[5-10] Thus, because atorvastatin and simvastatin can provide greater LDL-C reduction at lower doses than other statins, the risk for side effects may be reduced. However, since the overall incidence of side effects is rare for all statins even at higher doses, the potential increased risk with increased doses may not be clinically relevant.

As previously discussed in section V of this document, when considering the general population, use of any statin would not be precluded due to potentially harmful drug interactions.

Patient Outcomes Data
The next issue to be addressed is a controversial one—the issue of whether patient outcomes are resultant of a class effect for all statins or if it is specific to only certain drugs in the class. Each statin has been shown to reduce cardiovascular morbidity and mortality, but not all statins have been shown to reduce all-cause mortality. Atorvastatin, lovastatin, pravastatin, and simvastatin are the only drugs in this class that have all been shown in clinical trials to reduce all-cause mortality, but the strength of evidence on this outcome differs between these statins.

For atorvastatin, all-cause mortality was a specified primary outcome of the GREACE[18] study. The GREACE[18] study showed a statistically and clinically significant 43% relative reduction in risk (absolute risk reduction = 2.1%) with atorvastatin. The ASCOT-LLA[19] trial showed non-statistically significant differences in this outcome with atorvastatin; however, the trial was not designed or powered to detect a difference in all-cause death.

For lovastatin, a statistically significant reduction in total mortality was found in the ACAPS[26] trial, but this study was primarily designed to detect differences in 3-year changes in mean maximum intimal-medial thickness. Only 9 deaths total (1 in the lovastatin group and 8 in the placebo group) occurred out of the 919 subjects enrolled in the trial making it difficult to strongly conclude a decrease in total mortality benefit with this statin.

For pravastatin, the LIPID[33] study showed a statistically and clinically significant 22% relative reduction in risk (absolute risk reduction = 3.1%) in all-cause death with pravastatin versus placebo. However, the WOSCOPS,[30] PROSPER,[34] and ALLHAT-LLT[35] trials showed non-statistically significant differences in all-cause mortality, and this outcome was the primary outcome of ALLHAT-LLT[35] (WOSCOPS[30] and PROSPER[34] were not designed or powered to detect differences in all-cause mortality).

For simvastatin, total mortality was the primary outcome of the 4S[40] trial, which showed a statistically and clinically significant 30% relative reduced risk for this outcome (absolute risk reduction = 3.3%). Additionally, the HPS[41,42] showed a statistically and clinically significant 13% relative risk reduction (absolute risk reduction = 1.8%) in all-cause mortality (the primary outcome of the study) with simvastatin.

Given that greater than 3 agents in this class are supported with evidence (although to varying degrees) that they reduce overall mortality, one could argue that a class effect exists with the statins. However, if using the truly evidence-based approach, simvastatin appears to have the most consistent evidence to support this outcome benefit. Almost 25,000 patients were studied in the 4S[40] and HPS[41,42] trials collectively that were primarily designed to measure this outcome. Additionally, the theory of cholesterol independent or "pleiotropic effects" of the statins, while not supported with sound evidence, is interesting to consider for these drugs, especially since the HPS[41,42] showed clinical benefits from simvastatin even in patients with normal baseline LDL-C levels. However, recommendations at this time should not be made on theory. Further research would be needed to determine if there are differences in pleiotropic effects between the statins and if these differences directly result in superior clinical outcomes.

Despite the more consistent evidence for all-cause mortality reduction with simvastatin, other statins—atorvastatin, lovastatin, and pravastatin—have evidence that they too can reduce all-cause mortality. With the currently available evidence on atorvastatin, pravastatin, and simvastatin, it is difficult to determine any clear advantage of one statin over another in terms of all-cause mortality benefit. However, when comparing these three statins to lovastatin, the evidence supporting all-cause mortality benefit is clearer with atorvastatin, pravastatin, and simvastatin than with lovastatin since the all-cause mortality benefit seen with lovastatin was found in a smaller trial[26] that was primarily designed to detect differences in mean maximum intimal-medial thickness. The authors of this trial did not *a priori* set out to determine differences in all-cause mortality. Added, death only occurred in 9 patients total in this trial, which is a small number of patients to use when trying to extrapolate to the general population.

LDL-C Lowering Capacity

Atorvastatin and simvastatin provide the greatest LDL-C lowering capacity of all the statins, 39-60% and 26-47%, respectively.[5,10] At the recommended starting doses of each statin, atorvastatin and simvastatin provide greater LDL-L lowering capacity than the other statins.[5-10] Simvastatin also offers the widest dosage range (5mg to 80mg per day) of all the statins.[10] However, when considering use in the general population, all statins have the ability to effectively lower LDL-C in a dose-dependent manner.

Considering LDL-C lowering capacity, safety, and patient outcomes data (specifically reduction in all-cause mortality), brand versions of atorvastatin (Lipitor), pravastatin (Pravachol), and simvastatin (Zocor) offer significant clinical advantage in general use over other brands and generic products in the same class but are comparable to each other.

X. Recommendations

Medicaid should work with manufacturers of the brands of atorvastatin, pravastatin, and simvastatin on cost proposals so that at least one brand is selected as a preferred agent.

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Pharmacotherapy Review
HMG-CoA Reductase Inhibitor Combinations (AHFS Class 240608)

I. Overview

Cardiovascular disease is the most common cause of death among men and women in the United States. Nearly 13 million Americans have coronary heart disease resulting in 1.1 million myocardial infarctions (MI) annually, with 40% of those resulting in death.[1] Pathophysiologically, MI and acute coronary syndromes (ACS) result from a constellation of events that begins with an atherosclerotic plaque fissure followed by formation of a superimposed thrombus that partially or totally occludes the coronary artery.[2,3] The importance of thrombosis within this scheme is well-established and involves a complex interplay of both platelet-dependent processes and factors that stimulate the coagulation system.[4] The use of low dose aspirin (75mg to 325mg daily) following an MI has been conclusively shown to reduce subsequent MI, stroke, and death due to its antiplatelet activity.[5] Current treatment guidelines of secondary prevention of MI support the use of daily low dose aspirin therapy.[6]

Hydroxy-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (commonly referred to as "statins") effectively lower cholesterol and are considered first-line agents for treating hyperlipidemia. Statins work by inhibiting HMG-CoA reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate in an early step in the biosynthetic pathway for cholesterol. The inhibition of this enzyme decreases cholesterol synthesis causing an up-regulation of hepatic low-density lipoprotein (LDL) cholesterol receptors and enhanced clearance of circulating LDL cholesterol (LDL-C).

Given that CHD is the leading cause of death in the U.S. for both men and women, it seems prudent to screen for and aggressively treat patients with hyperlipidemia and to utilize antiplatelet therapy. Considering this, Bristol-Myers Squibb has packaged the HMG-CoA Reductase Inhibitor, pravastatin (Pravachol) and buffered aspirin tablets side by side into patient friendly blister cards (Pravigard PAC) that are intended to facilitate daily administration of these drugs.[7] The following table lists the products included in this review. This review encompasses all dosage forms and strengths.

Table 1.   HMG-CoA Reductase Inhibitor Combinations in this Review

Generic Name	Example Brand Name(s)
ASA/CAL CB/magnesium/pravastatin (otherwise known as buffered aspirin and pravastatin sodium)	Pravigard PAC

II. Indications for Buffered Aspirin and Pravastatin

According to package insert information, this product is approved for use in patients for whom treatment with both aspirin and pravastatin are appropriate.[7]

Pravastatin is indicated for primary and secondary prevention of cardiovascular events, primary hypercholesterolemia/mixed dyslipidemia, primary dysbetalipoproteinemia, regression of coronary atherosclerosis, heterozygous familial hypercholesterolemia in adolescents, and hypertriglyceridemia.[8]

Aspirin is indicated for reducing morbidity and mortality after ischemic stroke, transient ischemic attack (TIA), acute MI, unstable angina, and chronic stable angina. Aspirin is also indicated for prevention of recurrent MI and for patients who have undergone revascularization procedures when there is a pre-existing condition for which aspirin therapy is already indicated.[7]

III. Dosing and Administration of Buffered Aspirin and Pravastatin

The recommended dose of this product is 81-325mg/day of buffered aspirin plus 40mg/day of pravastatin. If LDL-C goal cannot be achieved with 40mg/day of pravastatin, then the dose of this product can be increased to 81-325mg/day of buffered aspirin plus 80mg/day of pravastatin (this is also the maximum dose). This product is also available as 81-325mg/day of buffered aspirin plus 20mg/day of pravastatin for those patients who may not need 40mg/day or greater to meet LDL-C goals.[7]

IV. Side Effects and Drug Interactions of Buffered Aspirin and Pravastatin

Since Pravigard PAC is a repackaging of pravastatin (Pravachol) and buffered aspirin tablets side by side into blister cards, Pravigard PAC would be expected to exhibit side effects and drug interactions comparable to those of pravastatin and aspirin as separate products (please refer to HMG-CoA Reductase Inhibitors Single Entity Agents review for more information on side effects of pravastatin).

V. Efficacy of Buffered Aspirin and Pravastatin

As previously mentioned, low dose aspirin (75mg to 325mg daily) has been conclusively shown to effectively reduce subsequent MI, stroke, and death.[5] Two main factors are typically considered when assessing efficacy of statins: 1) the capacity to reduce lipids, especially LDL-C since this cholesterol component has been identified as a major risk factor for CHD and is the target of NCEP-ATP III[9] guidelines; and 2) outcomes data, specifically morbidity parameters (including primary and secondary prevention) and mortality.

Table 2 provides the dose-based ability of pravastatin to lower LDL-C.

Table 2. Pravastatin's Dose-Dependent LDL-C Lowering Capacity[8]

Statin	Dose	LDL-C Reduction
Pravastatin	20mg/day	32%
	40mg/day	34%
	80mg/day	37%

Randomized controlled trials (RCTs) that measured patient-oriented outcomes (morbidity parameters and mortality) exist for pravastatin. PMS-CRP,[10] WOSCOPS,[11] CARE,[12] LIPID,[13] and PROSPER[14] all showed pravastatin to reduce cardiovascular morbidity and mortality in over 26,000 subjects collectively. The ALLHAT-LLT[15] trial (n= 10, 355) did not support the findings of the previous studies. However, when looking at all-cause mortality reduction with pravastatin, the evidence is inconsistent. The LIPID[13] study showed a statistically and clinically significant 22% relative reduction in risk (absolute risk reduction = 3.1%) in all-cause death with pravastatin versus placebo. However, the WOSCOPS,[11] PROSPER,[14] and ALLHAT-LLT[15] trials showed non-statistically significant differences in all-cause mortality, and this outcome was the primary outcome of ALLHAT-LLT[15] (WOSCOPS[11] and PROSPER[14] were not designed or powered to detect differences in all-cause mortality).

VI. Conclusions

When evaluating the addition of buffered aspirin and pravastatin (Pravigard PAC) for addition to the Alabama Medicaid preferred drug list, four main issues were considered:

1) Safety
2) Patient outcomes data (especially reduction in all-cause mortality)
3) LDL-C reduction
4) Evidence of improved compliance and thus outcomes with Pravigard PAC

Safety
Pravigard PAC is safe to use.   Safety profile is comparable to that of single entity pravastatin (Pravachol) and single entity buffered aspirin.

<u>Patient Outcomes Data</u>
As previously discussed in section V of this document, evidence of pravastatin's ability to reduce all-cause mortality is inconsistent. However, pravastatin has been conclusively shown to reduce cardiovascular morbidity and mortality parameters.   Aspirin has also been conclusively shown to reduce morbidity and mortality.[5]

<u>LDL-C Reduction</u>
Pravastatin can effectively lower LDL-C in a dose-dependent manner.

<u>Evidence of Improved Patient Compliance and thus Outcomes</u>
The makers of buffered aspirin and pravastatin (Pravigard PAC) packaged these individual drugs side by side into a blister pack to facilitate daily administration.[7] However, no evidence exists that this product is actually accomplishing its intended goal. Studies evaluating improved compliance and thus improved outcomes from improved compliance with this product have yet to be published.

Lastly, aspirin has been widely available in numerous generic formulations for many years and is readily available over-the-counter.

No brand HMG-CoA Reductase Inhibitor combination product (Pravigard PAC) offers significant clinical advantages over other brand or generic alternatives in general use.

VII.   Recommendations
No brand HMG-CoA Reductase Inhibitor combination product is recommended for preferred status.

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Pharmacotherapy Review
Miscellaneous Antilipemic Agents (AHFS Class 240692) Niacin Single Entity Agents

I. Overview

The mechanism of the lipid lowering effects of niacin is not completely understood. The primary mechanism of action seems to be inhibition of mobilization of free fatty acids from adipose tissues. Niacin also reduces hepatic synthesis of triglycerides (TG) and very low-density lipoprotein (VLDL), which in turn leads to decreased synthesis of low-density lipoprotein. Finally, niacin also increases high-density lipoprotein by reducing its catabolism.[1]

Lowering total cholesterol and low-density lipoprotein cholesterol (LDL-C) and raising high-density lipoprotein cholesterol (HDL-C) are important for many reasons. Deposition of cholesterol in the arterial walls is central to the pathogenesis of atherosclerosis in the coronary arteries. A direct correlation exists between total cholesterol, LDL-C, and the risk of developing coronary heart disease (CHD). Every 1% reduction in LDL-C results in a 1.7% decrease in the risk of a major coronary event. An inverse relationship exists between HDL-C and the risk for developing CHD—every 1mg/dL decrease in HDL-C results in a 2-3% increase in the risk of CHD.[1] Thus, pharmacotherapy that can lower total cholesterol and LDL-C while raising HDL-C is worthwhile. Hypertriglyceridemia (triglycerides > 150mg/dL) is also a risk factor for CHD and should be treated. Additionally, CHD statistics in the U.S. from 2002 indicated that 1.1 million adults experienced a new or recurrent myocardial infarction (MI) and 40% of those resulted in death. It is estimated that $100 billion is spent each year in the U.S. for direct and indirect costs associated with CHD.[2] Given that CHD is the leading cause of death in the U.S. for both men and women and that approximately 102 million Americans have total cholesterol levels greater than or equal to 200mg/dL (with 41 million American adults having levels of 240mg/dL or above),[3] it seems prudent to screen for and aggressively treat patients with hyperlipidemia.

Niacin is not as widely used as HMG-CoA Reductase Inhibitors (also known as "statins"), but it may be a useful treatment option for combined hyperlipidemias (increased triglycerides and LDL-C with decreased HDL-C). Niacin has been available generically and without a prescription for many years. Two branded products are the subject of this review and are listed in the Table 1 below. This review encompasses all dosage forms and strengths.

Table 1. Niacin Single Entity Agents in this Review

Generic Name	Example Brand Name(s)
Extended Release Niacin	Niaspan
Immediate Release Niacin	Niacor

II. Current Treatment Guidelines

The decision to treat hyperlipidemia generally follows the treatment guidelines of the Third Report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III.[4] Because LDL-C is the major atherogenic lipid component, NCEP-ATP III[4] focuses primarily on attaining goal LDL-C levels. While LDL-C is the primary treatment target, very elevated triglycerides should also be treated to avoid pancreatitis and reduce CHD risk. Finally, consideration should be given to treating low levels of HDL-C even if LDL-C goal is already reached.[4]

III. Comparative Indications for Niacin Single Entity Agents

The Food and Drug Administration (FDA) approved niacin for use in adjunct to diet for the reduction of total cholesterol and LDL-C in patients with primary hypercholesterolemia. Niacin is also indicated to reduce the risk of recurrent nonfatal myocardial infarction (MI) in patients with a history of MI and hypercholesterolemia. Table 4 summarizes the FDA-approved indications for each of the single entity niacin products in this review.

Table 4. FDA Approved Indications for Single Entity Niacin Agents[5,6]

Indication	Extended Release Niacin (Niaspan)	Immediate Release Niacin (Niacor)
As an adjunct to diet for the reduction of elevated TC and LDL-C in patients with primary hypercholesterolemia		✔
Hypertriglyceridemia	✔	✔
As an adjunct to diet for the reduction of TC, LDL-C, Apo B, TG, and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia	✔	
In combination with lovastatin for the treatment of primary hypercholesterolemia*	✔	
In combination with a bile acid binding resin for reduction of elevated TC and LDL-C	✔	

* Not indicated for initial therapy

IV. Comparative Pharmacokinetic Parameters of Single Entity Niacin Agents

The main difference between extended release niacin (Niaspan) and immediate release niacin (Niacor) is half-life; extended release niacin has a longer half-life. Niacin extended release and immediate release are rapidly and extensively absorbed from the gastrointestinal (GI) tract. Niacin extended release at a 1 to 2 gram dose reaches peak plasma concentration after 4 to 5 hours.[5] Immediate release niacin at a 1 gram dose reaches peak plasma concentration within 30-60 minutes.[6]

V. Comparative Drug Interactions with Single Entity Niacin Agents

No clinically [rated as 1 (major) or 2 (moderate)] drug interactions for the single entity niacin agents have been reported.[7,8] However, all niacin products should be used cautiously when administered concomitantly with HMG-CoA Reductase Inhibitors or fibric acid derivatives due to increased risk for rhabdomyolysis. While this does not preclude use of niacin with a statin or fibric acid derivative, additional care should be exercised to closely monitor the patient for any signs or symptoms of myopathy.

VI. Comparative Adverse Effects of Single Entity Niacin Agents

Patient intolerance tends to limit niacin use, particularly prostaglandin mediated vasodilatory (flushing of the neck and face, postural hypotension, tingling and itching) and GI side effects (nausea, vomiting, dyspepsia, and aggravation of peptic ulcer disease). Vasodilatory effects tend to be dose related and typically subside after several weeks of niacin therapy. Pre-medicating with aspirin 325mg or a non-steroidal anti-inflammatory drug may help to minimize flushing. It is also advisable to avoid hot beverages or alcohol around the time of niacin administration to minimize flushing. Extended release niacin (Niaspan) is typically taken at bedtime so flushing may be less bothersome because it occurs during sleep. However, care must be taken on the part of the patient if he/she is awakened by the flushing—the patient should get up slowly especially if feeling dizzy, faint, or taking antihypertensive medications.[5]

Increases in hepatic enzymes have been reported with niacin and thus periodic monitoring of liver function tests is recommended. Also, niacin can increase glucose levels and serum uric acid, so it should be used cautiously in patients with diabetes or gout.

Large head to head trials that compare tolerance of extended release niacin (Niaspan) to immediate release niacin (Niacor) have not been published. However, one small study of 223 men and women with hypercholesterolemia

compared Niaspan 1.5 grams/day to "plain niacin" (manufacturer unknown) 1.5 grams/day (given as 500mg three times daily) for 8 weeks.[9] Niaspan was comparable to plain niacin at increasing liver enzymes (AST increased 5% versus 4.8% for Niaspan and plain niacin, respectively; p > 0.05) and increasing fasting plasma glucose levels (4.8% versus 4.5% for Niaspan and plain niacin, respectively; p > 0.05). Statistically significant differences were seen for increases in uric acid (6% versus 16% for Niaspan and plain niacin, respectively; p = 0.0001) and for flushing events (576 versus 1,905 for Niaspan and plain niacin, respectively; p < 0.001). Flushing severity was reported by study participants to be slightly greater with Niaspan.[9]

In placebo-controlled trials of extended release niacin, flushing was reported by as many as 88% of patients. In comparison to immediate release niacin (manufacturer not specified), the proportion of patients who experienced flushing was similar; however, patients who took extended release niacin reported fewer flushing episodes.[5]

VII. Dosing and Administration of Single Entity Niacin Agents

Both extended release niacin and immediate release niacin should be initiated at a low dose and titrated slowly according to patient tolerance and response. In general, immediate release niacin is dosed twice daily or three times daily; extended release niacin can be dosed once daily (recommended at bedtime). While no studies have been conducted to compare patient compliance with immediate release versus extended release niacin, once daily dosing theoretically may improve compliance. However, in light of tolerance issues associated with both niacin products, this may not be a large consideration. Table 5 details the dosing guidelines for each agent in this review.

Table 5. Dosing and Administration of Single Entity Niacin Agents[5,6]

Agent	Dosing & Administration
Extended Release Niacin (Niaspan)	Initiate at 500mg/day (given as a single dose at bedtime after a low-fat snack) and continue for 4 weeks. Titrate to 1 gram/day (given as two 500mg tablets at bedtime) for the next 4 weeks. After week 8, dosage should be titrated to patient response and tolerance. If patient LDL-C or TG not at goal, can titrate dose to 1.5 grams/day (single dose at bedtime). Daily dose should not be titrated by more than 500mg/day every 4 weeks. Maximum recommended dose is 2 grams/day (as a single dose at bedtime).
Immediate Release Niacin (Niacor)	Initiate at 250mg/day (given as a single dose following the evening meal). Increase the frequency of dosing and the total daily dose every 4-7 days until goal LDL-C or TG is attained or if the therapeutic dose of 1.5-2 grams/day is reached (and if the patient tolerates). After 2 months of 1.5-2 grams/day, if goal LDL-C or TG is not reached, the dosage can be further titrated every 2-4 weeks to 1 gram three times daily. Usual adult dose is 1-2 grams two or three times daily. Higher doses are occasionally required but should not exceed 6 grams/day.

VIII. Comparative Effectiveness of the Single Entity Niacin Agents

Large head to head trials that directly compare extended release niacin (Niaspan) to immediate release niacin (Niacor) have not been published. However, one small study of 223 men and women with hypercholesterolemia compared Niaspan 1.5 grams/day to "plain niacin" (manufacturer unknown) 1.5 grams/day (given as 500mg three times daily) for 8 weeks.[9] Niaspan provided comparable efficacy (a non-statistically and non-clinically significant difference) to plain niacin as depicted in Table 6.

Table 6. Efficacy of Niaspan Compared to "Plain Niacin"[9]

Agent	TC	LDL-C	TG	HDL-C
Niaspan	8%	12%	16%	20%
Plain Niacin	8%	12%	18%	17%

In general, niacin, when compared to statins or fibric acid derivatives, is the most effective agent for increasing HDL-C. Niacin also effectively lowers LDL-C and triglycerides although to a lesser extent than statins and fibric acid derivatives, respectively. Table 7 details the cholesterol modifying effects of the agents in this review.

Table 7. Comparative Cholesterol Modifying Effects for Single Entity Niacin Agents[5,6]

Agent	TC	LDL-C	TG	HDL-C
Extended Release Niacin	↓ 5-12%	↓ 7-16%	↓ 16-38%	↑ 14-22%
Immediate Release Niacin	↓ 10-20%	↓ 10-20%	↓ 30-70%	↑ 20-35%

Landmark randomized controlled trials that measure patient-oriented outcomes (morbidity parameters and mortality) do not exist for any of the specific niacin products in this review. However, one landmark secondary prevention trial exists for niacin in general and is detailed in Table 8 below.

Table 8. Evidence for Niacin (Nicotinic Acid—exact product not specified in the trial)

Study	Sample	Duration	Results
CDP[10]	n = 8,341 men age 30-64 years with previous MI for the total study which looked at both niacin and clofibrate compared to placebo (n = 3,908 for niacin vs. placebo)	6 years	Compared to placebo, niacin 3g/day resulted in: • a reduced incidence of nonfatal MI (placebo= 12.2%, niacin = 8.9%; p < 0.004) • a comparable total mortality incidence (placebo = 25.4%; niacin = 24.4%; p was non-significant) A follow up of subjects 9 years after study completion showed:[11] • niacin reduced risk of all-cause mortality by 11% (placebo = 58.2%, niacin = 52%; p = 0.0004)

IX.   Conclusions

It has been shown that lowering cholesterol (including LDL-C) reduces cardiovascular risk. Because LDL-C is the major atherogenic lipid component, NCEP-ATP III[4] focuses primarily on attaining goal LDL-C levels. While LDL-C is the primary treatment target, very elevated triglycerides should also be treated to avoid pancreatitis and reduce CHD risk. Finally, consideration should be given to treating low levels of HDL-C even if LDL-C goal is already reached.[4]

Niacin is not as widely used as HMG-CoA Reductase Inhibitors[12] possibly because of a reduced LDL-C lowering capacity compared to statins and patient tolerance issues. While effective for hypertriglyceridemia, niacin is not as widely used as fibric acid derivatives,[12] again possibly due to tolerance issues and a reduced TG lowering capacity. Still, if the patient can tolerate niacin, it can be considered as a treatment option, either as monotherapy or combined with a statin or fibric acid derivative for lowering LDL-C, triglycerides and raising HDL-C.

Niacin has been available generically and without a prescription for many years. Neither brand name product in this review has been proven in large-scale randomized trials to reduce patient outcomes (morbidity and mortality). While extended release niacin may offer better tolerance than immediate release niacin, extended release niacin is

still associated with tolerability problems. Large randomized trials that definitively show improved tolerance of extended release niacin compared to immediate release niacin are lacking. Regardless of the niacin formulation, pre-treatment with aspirin or another NSAID is needed to help minimize vasodilatory side effects.

X.   Recommendations

In the absence of compelling evidence supporting a significant clinical advantage of either agent in this review over generics, OTC products, or other alternatives, no brand niacin single entity agents should be given preferred drug status.

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Pharmacotherapy Review
Miscellaneous Antilipemic Agents (AHFS Class 240692) Niacin Combination Agents

I.   Overview

Hydroxy-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (commonly referred to as "statins") work by inhibiting HMG-CoA reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate in an early step in the biosynthetic pathway for cholesterol. The inhibition of this enzyme decreases cholesterol synthesis causing an up-regulation of hepatic low-density lipoprotein cholesterol receptors and enhanced clearance of circulating LDL-C.

The mechanism of the lipid lowering effects of niacin is not completely understood. The primary mechanism of action seems to be inhibition of mobilization of free fatty acids from adipose tissues. Niacin also reduces hepatic synthesis of triglycerides (TG) and very low-density lipoprotein (VLDL), which in turn leads to decreased synthesis of low-density lipoprotein. Finally, niacin also increases high-density lipoprotein by reducing its catabolism.[1]

HMG-CoA reductase inhibitors are generally considered first-line agents for treating hyperlipidemia due to their ability to effectively lower total cholesterol and LDL-C. These agents also have the ability to moderately raise HDL-C. Niacin is not as widely used as HMG-CoA reductase inhibitors, but it may be a useful treatment option for combined hyperlipidemias (increased triglycerides and LDL-C with decreased HDL-C). Since niacin has a greater capacity than statins to raise HDL-C and lower TG, combining a statin and niacin may offer further benefit for modifying these cholesterol levels.

With this in mind, KOS Pharmaceuticals, Inc., has created a product that combines an HMG Co-A reductase inhibitor, lovastatin, and extended release niacin (Advicor™).[2] Table 1 lists the products included in this review. This review encompasses all dosage forms and strengths.

Table 1. Niacin Combination Agents in this Review

Generic Name	Example Brand Name(s)
Niacin Extended Release and Lovastatin	Advicor

II.   Current Treatment Guidelines

For a discussion of current treatment guidelines, please refer to the Niacin Single Entity Agents review.

III.   Indications for Combined Niacin Extended Release and Lovastatin

According to package insert information, combined niacin extended release and lovastatin is indicated for the treatment of primary hypercholesterolemia and mixed dyslipidemias. This product should not be used as initial therapy but instead is best utilized in patients who are already taking monotherapy lovastatin but require further TG lowering or HDL-C raising and would benefit from the addition of niacin; or in patients currently taking niacin monotherapy but would benefit from addition of lovastatin to further reduce LDL-C.[2]

IV.   Dosing and Administration of Combined Niacin Extended Release and Lovastatin

The usual recommended initial dose of extended release niacin is 500mg/day (given at bedtime). The typical recommended starting dose of lovastatin is 20mg/day. Extended release niacin can be titrated by 500mg every 4 weeks to a maximum 2,000mg/day. Lovastatin can be titrated every 4 weeks to a maximum of 80mg/day. However, the product in this review only contains 20mg of lovastatin per tablet. Dosing of this combination product (Advicor) should not exceed 2,000mg/40mg daily. The dose of Advicor can be titrated every 4 weeks according to patient response and tolerance based on the extended release niacin ingredient. This product should be taken at bedtime following a low fat snack.[2]

V. Drug Interactions of Combined Niacin Extended Release and Lovastatin

Since Advicor is a combination of niacin extended release and lovastatin, Advicor would be expected to exhibit drug interactions comparable to those of niacin extended release and lovastatin as separate products. (Please refer to the Niacin Single Entity Agents review and the HMG-CoA Reductase Inhibitors Single Entity Agents review for further information on drug interactions).

VI. Side Effects of the Combined Niacin Extended Release and Lovastatin

Table 2 lists the side effects of combined Niacin Extended Release and Lovastatin and its individual components.

Table 2. Comparative Side Effects[2]

Side Effect	Advicor	Niacin Extended Release	Lovastatin
Flushing	71%	65%	18%
Headache	9%	13%	5%
Abdominal pain	4%	1%	6%
Diarrhea	6%	9%	2%
Nausea	7%	12%	2%
Vomiting	3%	5%	0%
Myalgia	3%	5%	9%

VII. Efficacy of Combined Niacin Extended Release and Lovastatin

Two main factors are typically considered when assessing efficacy of antilipemic agents: 1) the capacity to reduce lipids, especially LDL-C since this cholesterol component has been identified as a major risk factor for CHD and is the target of NCEP-ATP III[3] guidelines (and secondarily to reduce TG and raise HDL-C); and 2) outcomes data, specifically morbidity parameters (including primary and secondary prevention) and mortality. Table 3 provides the dose-based ability of niacin extended release and lovastatin to modify cholesterol levels.

Table 3. Niacin Extended Release and Lovastatin's Dose-Dependent Cholesterol Modifying Effects[2]

Agent	Dose Niacin ER/Lovastatin	TC	LDL-C	TG	HDL-C
Niacin Extended Release and Lovastatin	1,000mg/20mg	NA*	↓ 30%	↓ 32%	↑ 20%
	1,000mg/40mg		↓ 36%	↓ 39%	↑ 20%
	1,500mg/40mg		↓ 37%	↓ 44%	↑ 27%
	2000mg/40mg		↓ 42%	↓ 44%	↑ 30%

* Information not provided in package insert for any dose

The ADVOCATE study[4] consisting of 315 subjects (mean age = 53 years, baseline LDL-C 191mg/dL and HDL-C 38mg/dL) compared efficacy of niacin extended release/lovastatin (1,000mg/40mg to 2,000mg/40mg) to atorvastatin 10-40mg/day and simvastatin 10-40mg/day for 16 weeks. Primary outcomes included mean percent change from baseline in LDL-C and HDL-C. The results are listed in Table 4 below.

Table 4. Comparative Results of the ADVOCATE study[4]

Study Point	Niacin Extended Release/Lovastatin	Atorvastatin	Simvastatin
Week 8	1,000mg/40mg	10mg/day	10mg/day
LDL-C	↓ 38%	↓ 38%	↓ 28%
HDL-C	↑ 20%	↑ 3%	↑ 7%
TG	↓ 30%	↓ 20%	↓ 18%
Week 12	1,500mg/40mg	20mg/day	20mg/day
LDL-C	↓ 42%	↓ 45%	↓35%
HDL-C	↑ 24%	↑ 4%	↑ 8%
TG	↓ 42%	↓ 30%	↓ 15%
Week 16	2,000mg/40mg	40mg/day	40mg/day
LDL-C	↓ 42%	↓ 49%	↓ 39%
HDL-C	↑ 32%	↑ 6%	↑ 7%
TG	↓ 49%	↓ 31%	↓ 19%

It is difficult to draw firm efficacy conclusions from this study since starting doses of atorvastatin and simvastatin were compared to non-starting doses of niacin extended release/lovastatin. Also, maximum doses of atorvastatin and simvastatin were not compared to the maximum dose of niacin extended release/lovastatin. The maximum niacin extended release/lovastatin dose decreased LDL-C less than atorvastatin and slightly more than simvastatin, but again we are left to ponder how the combination product would compare to maximum doses of atorvastatin and simvastatin. As expected, due to the niacin component, HDL-C was further increased and TG was further decreased with the combination product versus atorvastatin and simvastatin.

Randomized controlled trials (RCTs) that measured patient-oriented outcomes (morbidity parameters and mortality) do not exist for this combination product. However, for the lovastatin component of this product, this type of evidence is available. The ACAPS[5] trial showed a statistically significant reduction in total mortality with lovastatin 20-40mg/day versus placebo, but this study was primarily designed to detect differences in 3-year changes in mean maximum intimal-medial thickness. Only 9 deaths total (1 in the lovastatin group and 8 in the placebo group) occurred out of the 919 subjects enrolled in the trial making it difficult to strongly conclude a decrease in total mortality benefit with this statin. The ACAPS/TexCAPS[6] trial showed a 37% (95%CI 21-50) relative reduction in risk for first acute major coronary event (placebo =183, tx =116; p < 0.001) and a 40% (95%CI 17-57) relative reduction in risk of fatal or nonfatal MI (placebo =95, tx =57; p = 0.002), both of which are statistically and clinically significant. Niacin [not extended release niacin (Niaspan) as contained in Advicor] has also been shown in one landmark study, the CDP,[7] to reduce incidence of nonfatal MI (placebo= 12.2%, niacin = 8.9%; p < 0.004). A follow up of subjects 9 years after study completion showed that niacin reduced relative risk of all-cause mortality by 11% (placebo = 58.2%, niacin = 52%; p = 0.0004).[8]

VIII. Conclusions

When evaluating the addition of combined niacin extended release and lovastatin (Advicor) for addition to the Alabama Medicaid preferred drug list, three main issues were considered:

1) Safety
2) Patient outcomes data (especially reduction in all-cause mortality)
3) Comparative LDL-C lowering capacity to other antilipemic agents since LDL-C is still the primary treatment target of NCEP-ATP III[3]

Safety
Combined niacin extended release and lovastatin is safe although associated with the bothersome side effect of flushing due to the niacin extended release component.

Reduction in All-Cause Mortality
As previously discussed in section VII of this document, Advicor is lacking patient outcomes data. Lovastatin and niacin separately have some evidence that they reduce morbidity and mortality but this evidence is not as strong as with simvastatin or atorvastatin.

Comparative LDL-C Lowering Capacity
When comparing LDL-C lowering capacity of combined niacin extended release and lovastatin (Advicor) to other available HMG-CoA Reductase Inhibitors, only atorvastatin and simvastatin provide greater LDL-C lowering capacity at their maximum dose than Advicor at its maximum dose, 60% and 47%, respectively.[2,14,15] Also, to get the maximum dose of Advicor, the patient would have to take 2 tablets of this product compared to just 1 tablet of atorvastatin or simvastatin.

Lastly, niacin has been available generically and without a prescription for many years and lovastatin more recently became available generically. Most patients can be effectively treated with statin monotherapy and for those who may need additional TG lowering or HDL raising, generic niacin can be added to the statin.

IX. Recommendations

In the absence of compelling evidence supporting a significant clinical advantage of brand name niacin combination products over generics, OTC products, and other alternatives in general use, no brand niacin combination product is recommended for preferred status.

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Pharmacotherapy Review
Fibric Acid Derivatives (AHFS Class 240606)

I. Overview

Fibric acid derivatives work by increasing lipoprotein lipase activity and triglyceride clearance. These agents also increase hepatic oxidation of fatty acids, which decreases the secretion of triglyceride rich lipoproteins and enhances the breakdown of very low-density lipoprotein (VLDL). Finally, fibric acid derivatives may increase secretion of cholesterol into the bile.[1]

In short, fibric acid derivatives are the most effective pharmacotherapeutic option for lowering triglycerides (TG). Their main clinical use is for treating hypertriglyceridemia and for increasing low levels of high-density lipoprotein cholesterol (HDL-C). However, fibric acid derivatives can also be used to treat primary hypercholesterolemia but are not as widely used as HMG-CoA Reductase Inhibitors ("statins") because of reduced low-density lipoprotein cholesterol (LDL-C) capacity compared to statins.

Fibric acid derivatives have been available for a number of years (gemfibrozil and one strength of fenofibrate micronized are available generically); however three brand name products are the subject of this review and are listed in Table 1 below. This review encompasses all dosage forms and strengths.

Table 1. Fibric Acid Derivatives in this Review

Generic Name	Example Brand Name(s)
Fenofibrate, micronized	Lofibra*
Fenofibrate	Tricor
Gemfibrozil	Lopid*

* available generically in at least one dosage form or strength

The decision to treat hyperlipidemia generally follows the treatment guidelines of the Third Report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III.[2]   Because LDL-C is the major atherogenic lipid component, NCEP-ATP III focuses primarily on attaining goal LDL-C levels. However, this treatment guideline also classifies triglycerides as depicted in Table 2 below.

Table 2. NCEP-ATP III Classification of Triglyceride Levels[2]

Triglycerides	Classification
< 150 mg/dL	Normal
150-199 mg/dL	Borderline High
200-499 mg/dL	High
≥ 500 mg/dL	Very High

Hypertriglyceridemia (triglycerides > 150mg/dL) is also a risk factor for coronary heart disease (CHD) and should be treated. Very high triglycerides can increase risk for pancreatitis. High triglycerides should be treated with patient weight reduction, a low fat and cholesterol diet, regular exercise, smoking cessation, alcohol restriction, and pharmacotherapy if needed.   While the primary aim of NCEP-ATP III is lowering LDL-C to goal levels, the guideline also identifies non-HDL-C as a secondary goal if TG is still greater than 200mg/dL even after LDL-C goal is reached. The goal for non-HDL-C should be set at 30mg/dL higher than the LDL-C goal. Non-HDL-C is calculated as total cholesterol minus HDL-C.[2]

As mentioned above, fibric acid derivatives can also be used to help raise HDL-C. This is important because an inverse relationship exists between HDL-C and the risk for developing CHD—every 1mg/dL decrease in HDL-C results in a 2-3% increase in the risk of CHD.[1]

II. Comparative Indications for Fibric Acid Derivatives

The Food and Drug Administration (FDA) has approved fibric acid derivatives as an adjunct to diet for hyperlipidemias. The following table summarizes the FDA-approved specific indications for each of the fibric acid derivatives in this review.

Table 3. FDA Approved Indications for Single Entity Niacin Agents[3-5]

Indication	Fenofibrate, micronized (Lofibra)	Fenofibrate (Tricor)	Gemfibrozil (Lopid)
Treatment of primary hypercholesterolemia or mixed dyslipidemia	✔	✔	✔ *
Hypertriglyceridemia	✔	✔	✔

* To reduce the risk of developing CHD in patients specifically with type II b lipoprotein disorder who do not have a history or symptoms of CHD and who have low HDL-C in addition to increased LDL-C and TG levels. Gemfibrozil is not indicated for patients with low HDL-C as their only lipid abnormality.

III. Comparative Pharmacokinetic Parameters of Fibric Acid Derivatives

The two formulations of fenofibrate in this review have been shown to be bioequivalent. Plasma concentrations of fenofibrate 54mg and 160mg (Tricor) are equivalent to fenofibrate micronized 67mg and 200mg (Lofibra), respectively. Peak plasma concentrations with fenofibrate and fenofibrate micronized occur 6-8 hours after administration and the extent of absorption of both products is increased by 35% when taken with food. Serum protein binding is approximately 99% and steady state is reached within 5 days for both fenofibrate products. Both products are mainly excreted via the urine. The half-life for both fenofibrate and fenofibrate micronized is 20 hours, allowing for once daily dosing for both products.[3-4]

Gemfibrozil reaches peak plasma concentration at 1-2 hours after administration. Rate and extent of gemfibrozil absorption are significantly increased if taken 30 minutes prior to a meal. Gemfibrozil is highly protein bound and approximately 70% is excreted via the urine. Half-life for gemfibrozil is shorter than fenofibrate products and thus twice daily dosing is needed.[5]

IV. Comparative Drug Interactions with Fibric Acid Derivatives

Each fibric acid derivative should be administered cautiously with HMG-CoA Reductase Inhibitors due to increased risk for myopathy and rhabdomyolysis. Fenofibrate micronized, fenofibrate, and gemfibrozil can each interact with warfarin and thus proper anticoagulation monitoring should be exercised if these agents are used concomitantly. Also, fenofibrate and fenofibrate micronized should be used cautiously with cyclosporine (can cause decreased levels of cyclosporine and thus decreased effectiveness; management is to monitor and adjust cyclosporine dose if needed).[3-5]

V. Comparative Adverse Effects of Fibric Acid Derivatives

Fibric acid derivatives are fairly well tolerated. No clear differences seem to exist with regard to side effects between the drugs in this class. Myopathy and rhabomyolysis has been rarely reported with fibric acid derivative therapy. Table 4 below lists adverse effects reported with the various fibric acid derivatives. Incidences of adverse effects are listed as percentages with the placebo incidence listed in parentheses.

Table 4. Adverse Reactions (%) Reported with the Fibric Acid Derivatives[3-5]

Adverse Effect	Fenofibrate micronized* (placebo)	Fenofibrate* (placebo)	Gemfibrozil (placebo)
Abdominal pain	4.6% (4.4%)	4.6% (4.4%)	19.6% (11.9%)
Headache	3.2% (2.7%)	3.2% (2.7%)	1.2% (1.1%)
Abnormal liver function test	7.5% (1.4%)	7.5% (1.4%)	R[#]
Diarrhea	2.3% (4.1%)	2.3% (4.1%)	7.2% (6.5%)
Nausea	2.3% (1.9%)	2.3% (1.9%)	2.5% (2.1%)
Constipation	2.1% (1.4%)	2.1% (1.4%)	1.4% (1.3%)
CPK increase	3.0% (1.4%)	3.0% (1.4%)	R[#]

* Dosage equivalent to 200mg of each product
# Reported but no incidence provided

VI. Dosing and Administration of Fibric Acid Derivatives

Table 5 summarizes the dosing and administration of each fibric acid derivative.

Table 5. Comparative Dosing and Administration of Fibric Acid Derivatives[3-5]

Agent	Dosing & Admistration
Fenofibrate micronized	For primary hypercholesterolemia or mixed hyperlipidemia, initial dose is 200mg daily. For hypertriglyceridemia, initial dose is 67-200mg daily. Dosage should be individualized according to patient response. Maximum dose is 200mg/day. Best to administer with a meal.
Fenofibrate	For primary hypercholesterolemia or mixed hyperlipidemia, initial dose is 160mg daily. For hypertriglyceridemia, initial dose is 54-160mg daily. Dosage should be individualized according to patient response. Maximum dose is 160mg/day. Best to administer with a meal.
Gemfibrozil	Initiated and maintained at 600mg twice daily (maximum dose 1,200mg/day). Best to administer 30 minutes prior to a meal.

VII. Comparative Effectiveness of the Fibric Acid Derivatives

Two main factors are typically considered when assessing efficacy of fibric acid derivatives: 1) the capacity to reduce lipids, especially TG since this is the cholesterol component these agents are mainly used to lower in clinical practice (along with secondarily modifying TC, LDL-C, and HDL-C) and 2) outcomes data, specifically morbidity parameters (including primary and secondary prevention of CHD) and mortality. Table 6 compares the cholesterol modifying effects.

Table 6. Fibric Acid Derivative's Effects on Cholesterol[3-5]

Agent	TG	LDL-C	HDL-C	TC
Fenofibrate micronized	↓ 29-55%	↓ 20%*	↑ 11-23	↓ 9-19
Fenofibrate	↓ 29-55%	↓ 20%*	↑ 11-23	↓ 9-19
Gemfibrozil	↓ 20-50%	↓ 0-15%*	↑ 15-20%	↓ 15%

* LDL-C may actually increase

One small randomized crossover trial[6] directly compared cholesterol-lowering effects of fenofibrate micronized (200mg/day) to gemfibrozil (900mg/day) in 21 patients (age 45-70 years) with hyperlipidemia (specifically type IIa and IIb). Fenofibrate micronized and gemfibrozil caused similar reductions in TG (54% and 46.5%, respectively; $p > 0.05$) and increases in HDL-C (9% and 9%, respectively; $p > 0.05$). Reductions in LDL-C and TC were greater with fenofibrate micronized compared to gemfibrozil (LDL-C: 27% versus 16%, respectively; $p = 0.0117$) and (TC: 22% versus 15%, respectively; $p = 0.0148$). However, this trial is limited by the fact that maximum dose fenofibrate

micronized was compared against subtherapeutic doses of gemfibrozil (recommended dose of gemfibrozil is 600mg twice daily).

Randomized controlled trials (RCTs) that measured patient-oriented outcomes (morbidity parameters and mortality) exist only for gemfibrozil. Fenofibrate micronized and fenofibrate have not been studied for their effect on morbidity and mortality. The DAIS trial[7] was not included in this review because it measured disease-oriented evidence (outcomes included LDL particle size and mean lumem diameter) and not explicit morbidity and mortality parameters, and it was performed in the diabetic population and not the general population. Major RCTs that measured patient-oriented outcomes are summarized below for gemfibrozil.

Table 7. Evidence for Gemfibrozil

Study	Sample	Duration	Results
HHS[8]	n = 4,081 men age 40-55 years with a baseline TC of 290mg/dL and a non-HDL-C $\geq$ 200mg/dL	5 years	Compared to placebo, gemfibrozil 600mg twice daily resulted in: • 34% (95%CI 8.2 – 52.6) ↓ in coronary heart disease* • no significant difference between groups in total mortality A post-trial evaluation done 3.5 years after the HHS showed[9]: • no difference in cardiovascular or total mortality (total mortality was slightly higher in the gemfibrozil group, but this was statistically nonsignificant) An ancillary study (Helsinki II)[10] in patients with CHD showed that although nonsignificant, there were more nonfatal MIs, cardiac deaths and non-cardiac deaths in the gemfibrozil group.
VA-HIT[11]	n = 2,531 men age < 74 years with CHD and a baseline HDL-C $\leq$ 40mg/dL and LDL-C $\leq$ 140mg/dL	5.1 years	Compared to placebo, gemfibrozil 600mg twice daily resulted in: • 22% (95%CI 7-35) ↓ risk for nonfatal MI or death due to CHD (placebo = 21.7%, tx = 17.3%; p = 0.006)* • 24% (95%CI 11-36) ↓ risk for nonfatal MI, death due to CHD, or confirmed stroke (placebo = 26%, tx = 20.4%; p < 0.001) • a nonsignificant difference was seen in all-cause mortality (placebo = 17.4%, tx = 15.7%; p = 0.23) A post-trial analysis[12] showed that gemfibrozil 600mg twice daily resulted in: • 11% (95%CI 2-19) ↓ risk for CHD events for every 5mg/dL increase in HDL-C (p = 0.02)

* Primary outcome of the study

VIII.   Conclusions

It has been shown that lowering cholesterol (including LDL-C) reduces cardiovascular risk. Because LDL-C is the major atherogenic lipid component, NCEP-ATP III focuses primarily on attaining goal LDL-C levels. While LDL-C is the primary treatment target, very elevated triglycerides should also be treated to avoid pancreatitis and reduce CHD risk. Finally, consideration should be given to treating low levels of HDL-C even if LDL-C goal is already reached.

Fibric acid derivatives are not as widely used as HMG-CoA Reductase Inhibitors[13] probably because of a reduced LDL-C lowering capacity compared to statins. The main place in therapy for fibric acid derivatives is for treating hypertriglyceridemia, of which they have a greater capacity to reduce TG compared to statins.

Gemfibrozil and fenofibrate micronized (134mg capsules) have been available generically for years. There are no major clinically relevant differences between gemfibrozil, fenofibrate micronized, and fenofibrate with regard to triglyceride lowering efficacy and safety. Gemfibrozil is supported by clinical trials that showed reduction in patient-oriented outcomes (CHD disease and death from CHD); however, no benefit in reduction of all-cause mortality has been shown with gemfibrozil (or any other agent in this review) as has been shown with HMG-CoA Reductase Inhibitors.

IX.   Recommendations

In the absence of compelling evidence supporting a significant clinical advantage of any agent in this review over available generics or other alternatives in general use, no brand fibric acid derivative is recommended for preferred status.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee
Pharmacotherapy Reviews

Section II Table of Contents

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Anti-hypertensive Classes, Selected AHFS Groups

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Selected AHFS Anti-hypertensive Classes
December 10, 2003

I. Overview

Hypertension is the most common disease-specific reason that an American will visit a physician and it is one of the leading causes of morbidity and mortality world-wide; it affects approximately 50 million Americans and one billion people world-wide and generally increases with age.[1,2,3] The "modern" era of hypertension management was ushered in with the 1960's when a study of the treatment of mild hypertension was conducted in the Veterans Administration system.[4] The findings initiated and emphasized the importance of controlling blood pressure and establishing guidelines for hypertension management.[4] This led to the development of the National High Blood Pressure Education Program (NHBPEP) in 1972 and then in 1977, in coordination with NHBPEP, the formation of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC) all administered through the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH).[3]

Definition of Hypertension
Hypertension is a disorder of circulatory regulation. The hallmark of essential hypertension is increased peripheral arterial resistance.[1,5] The definition of what constitutes hypertension continues to be refined. The most current guidelines are in the JNC 7 Report published in May 2003.[3] The blood pressure classifications are summarized below.

Classification of Blood Pressure (BP) for Adults Aged 18 years old and Older[3]			
BP Classification	**Systolic BP (mmHg)**	**and/or**	**Diastolic BP (mmHg)**	**Drug Treatment Indicated**
Normal	<120	and	<80	No
Prehypertension	120-139	or	80-89	No*
Stage 1 hypertension	140-159	or	90-99	Yes
Stage 2 hypertension	≥160	or	≥100	Yes

*Drugs are indicated for compelling indications.

The majority of hypertension is "essential" and most agree that the underlying causes and predispositions are multifactorial.[1,2] This, in part, accounts for the mechanistically diverse group of drug classes used to treat hypertension. The primary reason for attempts to "normalize" blood pressure is to prevent major adverse cardiovascular events.   This relationship is continuous, consistent, and independent of other risk factors; the higher the blood pressure, the more likely the chance of myocardial infarction (MI), heart failure, stroke and kidney disease. Lowering blood pressure over the long term decreases these risks.[3]

II. Treatment Guidelines – The JNC 7 Report

Lifestyle modifications are the first line of therapy in prehypertension and stage 1 and stage 2 hypertension. Following the best efforts to change lifestyle, without blood pressure control, drug therapy is indicated. Thiazide-type diuretics should be used as initial therapy for most patients with uncomplicated hypertension, either alone or in combinations with one of the other classes: ACE Inhibitors, angiotensin II receptor blockers (ARBs), beta blockers, or calcium channel blockers because it is these classes that have been found to reduce the complications of hypertension in randomized controlled trials. Certain, high-risk conditions are compelling indications for the initial use of other antihypertensive drug classes. (See Table 1) In addition, most patients will require two or more anti-hypertensive medications to achieve their goal blood pressure. A second drug should be added when the first drug does not adequately control the blood pressure to goal. When blood pressure is more than 20/10mmHg above goal, consideration should be given to initiation of multi drug therapy (two separate prescription drugs or a fixed-dose combination), one of which should be a thiazide-type diuretic.[3]

Table 1

JNC-7 Compelling Indications for Individual Drug Classes[3]						
High Risk Conditions with Compelling Indications*	Diuretic	Beta Blocker	ACE Inhibitor	ARB	CCB	Aldosterone Antagonist
Heart Failure	√	√	√	√		√
Post-MI		√	√			√
High coronary disease risk	√	√	√		√	
Diabetes	√	√	√	√	√	
Chronic kidney disease			√	√		
Recurrent stroke prevention	√		√			

*The compelling indication is managed in parallel with the blood pressure. Compelling indications for antihypertensive drugs are based on benefits from outcome studies or existing clinical guidelines.[3]

The drugs classes being considered by Alabama Medicaid Pharmacy and Therapeutics Committee to be available for the treatment of hypertension include those listed below. This review encompasses all dosage forms and strengths.

Beta-Adrenergic Blocking Agents (Beta-Blockers) AHFS Class 242400
      General
      Intrinsic sympathomimetic activity (ISA)
      Alpha-blocking activity

Calcium Channel Blocking Agents AHFS Class 242800
      Non-dihydropyridine
      Dihydropyridine

Diuretics AHFS Class 402800
      Thiazide diuretics
      Loop diuretics
      Potassium-sparing diuretics

Hypotensive Agents AHFS Class 240800
      Central Alpha-Adrenergic Agonists
      Peripheral Adrenergic Neuron Antagonists
      Direct Vasodilators

Hypotensive Combination Agents AHFS Class 240800

Beta-Adrenergic Blocking Agents (Beta-Blockers) AHFS Class 242400
This review encompasses all dosage forms and strengths.

I. Indications and Availability

Generic Name	Example Brand Names	Generic Available*[11,12]	FDA Approved Indications[11,13,14-28]
Acebutolol HCl	Sectral	Yes	HTN Arrhythmias
Atenolol	Tenormin	Yes	HTN Angina Acute MI
Betaxolol HCl	Kerlone	Yes	HTN
Bisoprolol fumarate	Zebeta	Yes	HTN
Carteolol HCl	Cartrol	No	HTN
Carvedilol	Coreg	No	HTN CHF Left ventricular dysfunction post MI
Labetalol HCl	Normodyne Trandate	Yes	HTN
Metoprolol succinate	Toprol XL	No	HTN Angina CHF
Metoprolol tartrate	Lopressor	Yes	HTN Angina Acute MI (IV form)
Nadolol	Corgard	Yes	HTN Angina
Penbutolol sulfate	Levatol	No	HTN
Pindolol	Visken (no longer available in brand name; generic only)	Yes	HTN
Propranolol HCl-immediate release	Inderal	Yes	HTN Arrhythmias Post MI Hypertrophic subaortic stenosis Migraine prophylaxis Essential tremor Angina Pheochromocytoma
Propranolol-extended release	Inderal LA	Yes	Same indications as propranolol-immediate release except not indicated for: arrhythmias, essential tremor or pheochromocytoma.
	Innopran XL	No	HTN
Timolol maleate	Blocadren	Yes	HTN Migraine headache Post MI

*Generics available in at least one dosage form or strength.

II. Comparative Pharmacology/Pharmacokinetic Parameters (See Table 2)

Mechanism of Action:
Beta blockers lower blood pressure by the following mechanisms:[6]

> Decrease cardiac output, contractility and heart rate
> Diminish sympathetic reflex
> Decrease release of adrenergic substances centrally
> Inhibit peripheral epinephrine release
> Decrease renin release

There are important pharmacologic and pharmacokinetic differences between the different beta blocking agents, including intrinsic sympathomimetic activity (ISA), beta selectivity and membrane stabilizing effects; however, there is no difference in their clinical antihypertensive efficacy.[7] Despite differences in pharmacologic and pharmacokinetic properties, the anti-hypertensive effect of all the beta blockers is of sufficient duration to permit twice daily administration. Beta blockers provide effective therapy for all grades of hypertension.[8]

Intrinsic Sympathomimetic Activity
Beta blockers differ in whether they have Intrinsic Sympathomimetic Activity. Theoretically, beta blockers that have ISA can lower blood pressure with less decrease in heart rate at rest and are preferred in patients who develop bradycardia that is symptomatic or postural hypotension with other beta blockers. Beta blockers *without* ISA are preferred in hypertensive patients with angina or a history of MI.[7,9,10]

Beta Blockers that have ISA:[7,9,10]
> Acebutolol
> Carteolol
> Penbutolol
> Pindolol

Non-selective (B-1 and B-2) vs Selective (B-1) Beta Blockers
Non-selective beta blockers include carteolol, nadolol, penbutolol, pindolol, propranolol, and timolol.
Cardioselective or B-1 selective beta blockers include acebutolol, atenolol, betaxolol, bisoprolol and metoprolol. These B-1 selective agents lose selectivity as the dose is increased and it is still possible that even at low doses bronchospasms can occur.[9]

Lipophilicity
Beta blockers differ in their degree of lipophilicity. **Propranolol** is very lipophilic, while **atenolol** is weakly lipophilic. It is this lipophilicity that determines to what extent the beta-blocker crosses the blood-brain barrier. Despite these differences in concentrations in the central nervous system, there is no difference in their hypotensive effectiveness. However, lipophilicity and its contribution to central nervous system side effects is a topic surrounded by debate, with atenolol being perhaps the better tolerated.[7]

Membrane Stabilizing Properties
All beta blockers are capable of exerting a membrane-stabilizing action on cardiac cell membranes with large enough doses. However, this activity is important for the antiarrhythmic properties of beta blockers and not hypertension.[7]

Beta blockers with Alpha Blocking Properties
Labetalol is a non-selective beta blocker with minimal ISA in addition to alpha blocking properties. It decreases blood pressure more promptly as compared to other beta blockers and is thought to be equally effective in Caucasian and African American populations. Carvedilol is a non selective beta blocker with alpha blocking properties *without* ISA and is indicated in hypertension and heart failure.[9]

Table 2

Pharmacologic/Pharmacokinetic Properties of Beta-Adrenergic Blocking Agents[9,11]				
Beta-Adrenergic Blocking Agents	**Intrinsic Sympathomimetic Activity (ISA)**	**Adrenergic-Receptor Blocking Activity**	**Lipid Solubility**	**Membrane Stabilizing Ability**
Acebutolol HCl	+	Selective*	Low	+[†]
Atenolol	0	Selective*	Low	0
Betaxolol HCl	0	Selective*	Low	+
Bisoprolol fumarate	0	Selective*	Low	0
Carteolol HCl	++	Non-selective	Low	0
Carvedilol	0	Non-selective beta/alpha	Moderate/High‡	Not available‡
Labetalol HCl	+	Non-selective beta/alpha	Low ‡	+[†]‡
Metoprolol succinate	0	Selective*	Moderate	0[†]
Metoprolol tartrate	0	Selective*	Moderate	0[†]
Nadolol	0	Non-selective	Low	0
Penbutolol sulfate	+	Non-selective	High	0
Pindolol	+++	Non-selective	Low	0
Propranolol HCl	0	Non-selective	High	++
Timolol maleate	0	Non-selective	Low to moderate	0

0 – none   *At high doses loses selectivity.
+ - low   [†] Detectable only at doses greater than required for beta blockade.
++ - moderate   ‡ Per manufacturer's package information.[19,20]
+++ - high

III. Safety Considerations

Contraindications of Beta Blockers[7,11,13]
        Asthma (use of a nonselective beta blocker)
        Cardiogenic shock
        Decompensated heart failure
        Heart block (2nd or 3rd degree)
        Hypersensitivity to beta blockers or any components
        Severe COPD (use of a nonselective beta blocker)
        Sinus bradycardia
        Systolic blood pressure$\leq$100 mmHg (metoprolol)[1,2]

Special Precautions of Class
Diabetic patients should use caution when taking these agents as they can increase blood glucose as well as mask the signs of hypoglycemia. Cardioselective agents may be safer in these patients. Beta blockers may also mask signs of hyperthyroidism (i.e. increased heart rate). A slow titration off therapy due to beta blocker withdrawal syndrome is necessary.[7,11,13] Beta blockers are one of the preferred drug classes in some pregnant women due to the safety for the fetus.[3]

Comparative Side Effects

Although many sources state that beta blockers are generally well tolerated[10], side effects of beta blockers are possible. Some of the most common side effects include: bradycardia, arrhythmias, heart failure, bronchospasm, decreased circulation peripherally, dizziness, drowsiness, headache, mental depression, diarrhea, constipation, nausea, vomiting, flatulence, rash, pruritis, sexual dysfunction, and thrombocytopenia.[11,13] The existence and occurrence of a few of these side effects as compared to placebo is a disputed topic. While some experts agree that there is no convincing evidence that less lipid-soluble beta blockers have fewer adverse effects on the central nervous system,[29] disagreement occurs among experts regarding depression, fatigue and sexual dysfunction.[9]

Significant Drug Interactions[11,30, 31]

Clinically important drug interactions exist for this class of drugs. Clinically significant drug interactions [rated as 1 (major severity) or 2 (moderate severity) and well documented] for beta blockers are listed below.

> Barbiturates
> Cimetidine (metoprolol, propranolol, timolol)
> Clonidine
> Cyclosporine (carvedilol)
> Diltiazem
> Ergot alkaloids
> Hydralazine (metoprolol, propranolol)
> Phenothiazines (propranolol, pindolol)
> Prazosin
> Propafenone (metoprolol, propranolol)
> Quinidine
> Rifamycins (bisoprolol, metoprolol, propranolol)
> SSRIs (carvedilol, metoprolol, propranolol)
> Thioamines (metoprolol, propranolol).
> Verapamil

IV. Dosing and Administration Considerations

Generic Name	Example Brand Name	Usual Dose in Hypertension[11,13]	Frequency[11,13]
Acebutolol HCl	Sectral	200-1200mg	QD-BID
Atenolol	Tenormin	25-100mg	QD-BID
Betaxolol HCl	Kerlone	5-40mg	QD
Bisoprolol fumarate	Zebeta	5-20mg	QD
Carteolol HCl	Cartrol	2.5-10mg	QD
Carvedilol	Coreg	12.5mg-50mg	BID
Labetalol HCl	Normodyne, Trandate	200-1200mg	BID
Metoprolol succinate	Toprol XL	25-200mg	QD
Metoprolol tartrate	Lopressor	50-200mg	QD-BID
Nadolol	Corgard	20-320mg	QD
Penbutolol sulfate	Levatol	20mg	QD
Pindolol	Visken (no longer available in brand name; generic only)	10-60mg	BID
Propranolol HCl-immediate release	Inderal	40-200mg	BID-QID
Propranolol-extended release	Inderal LA	60-240mg	QD
	Innopran XL	80-120mg	HS

| Timolol maleate | Blocadren | 10-60mg | BID |

V. Comparative Effectiveness

In 1993 and again in 1997, the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure recommended that low-dose diuretics and beta blockers as first line treatment of hypertension.[32,33] These recommendations were based on numerous clinical trials that showed their benefits. [34] All beta blockers that are marketed for oral treatment of hypertension are considered to be equally effective.[29]

Guideline Recommendations
JNC-7
Clinical trial outcomes data prove that lowering blood pressure with several classes of drugs, including beta blockers will reduce the complications of hypertension. Compelling indications for using beta blockers include heart failure, post-MI, high coronary disease risk and diabetes. The African American population may be less sensitive to the blood pressure lowering effects of monotherapy with beta blockers. Beta blockers can be useful in the treatment of atrial tachyarrhythmias and atrial fibrillation, migraine headaches, short term thyrotoxicosis, essential tremor or perioperative hypertension.[3]

2003 WHO/ISH (World Health Organization/International Society of Hypertension Statement on Hypertension
The data regarding the use of beta blockers conclusively demonstrates reduction in both morbidity and mortality.[35]

2003 ESH/ESC Guidelines for Management of Arterial Hypertension
Beta-blockers are suitable for initiation and maintenance of therapy. Beta blockers are one of the preferred drug classes in some pregnant women.[36,37]

Management of High Blood Pressure in African Americans Consensus Statement
As monotherapy, beta blockers and angiotensin converting enzyme (ACE) inhibitors may produce less blood pressure-lowering effects in African Americans than in Caucasians.[38]

Treatment Guidelines from the Medical Letter
Beta blockers are effective from treatment of hypertension and have been shown in large scale trials to decrease mortality in patients with hypertension. Beta blockers may be less effective in the African American population (similar to ACE Inhibitors and ARBs.) Beta blockers may be less effective than a diuretic in controlling blood pressure in elderly patients.[9]

VI. Conclusions

Overwhelming evidence supports better blockers' beneficial effects in the treatment of hypertension. While there are differences in pharmacologic and pharmacokinetic properties between beta blockers, there is no difference in their clinical antihypertensive efficacy. Currently, there is an absence of evidence that one or more agents have a significant clinical advantage in the treatment of hypertension and numerous generic products are available. All brand products within the class reviewed are comparable to each other and to the generic products in that class and offer no significant clinical advantage over other alternatives in general use.

VII. Recommendations
No brand beta blocker is recommended for preferred status.

Calcium Channel Blocking Agents AHFS Class 242800

This review encompasses all dosage forms and strengths.

I. Indications and Availability

Generic Name	Example Brand Names	Generic Available*[11,12]	FDA Approved Indications[11,13,39-55]
Amlodipine besylate	Norvasc	No	HTN Angina (prinzmetal's, variant or chronic stable angina)
Diltiazem- sustained release	Cardizem SR	Yes	HTN
Diltiazem- extended release	Cardizem LA	No	HTN
	Cardizem CD	Yes	HTN Angina (chronic stable angina or due to vasospasm)
	Dilacor XR	Yes	HTN, Angina (chronic stable angina)
	Tiazac	Yes	HTN, Angina (chronic stable angina)
Felodipine	Plendil	No	HTN
Isradipine	Dynacirc	No	HTN
	Dynacirc CR	No	HTN
Nicardipine	Cardene	Yes	HTN Angina (chronic stable angina)
	Cardene SR	No	HTN
Nifedipine	Adalat CC	Yes	HTN
	Procardia XL	Yes	HTN Angina
Nisoldipine	Sular	No	HTN
Verapamil- immediate release	Calan	Yes	HTN Angina Arrhythmias
Verapamil- sustained release	Verelan	Yes	HTN
	Calan SR	Yes	HTN
	Isoptin SR	Yes	HTN
Verapamil-controlled onset-extended release	Covera HS	No	HTN, Angina
	Verelan PM	No	HTN

*Generics available in at least one dosage form or strength.

AHFS classifies the following agents as calcium channel blockers. However, they are not indicated in the treatment of hypertension they may be reviewed at a future date.
Bepridil (Vascor) is not indicated for HTN and will not be reviewed for the hypertension indication.[11,13,55]
Nimodipine (Nimotop) is not indicated for HTN and will not be reviewed for the hypertension indication.[11,13,56]

Adalat and **Procardia** (nifedipine) and **Cardizem** (diltiazem) are immediate release products and are only indicated for angina and therefore will not be reviewed for the hypertension indication. [11,13,55,56,5758-60]

II. Comparative Pharmacokinetic/Pharmacology Parameters

Mechanism of Action:
Promote vasodilation by preventing intracellular influx of calcium, which decreases peripheral resistance.[9,10]

Calcium Channel Blocker Classification
There are two groups of calcium channel blockers, the non-dihydropyridines and the dihydropyridines. Verapamil and diltiazem comprise the non-dihydropyridine group. Amlodipine, felodipine, isradipine, nicardipine, nifedipine and nisoldipine comprise the dihydropyridine group. (See Table 3 below.) They are all similar in their antihypertensive effectiveness, but differ somewhat in their pharmacokinetic and pharmacodynamic effects. (See Table 1 and Table 2 in Appendix A for a summary of these differences.) For example, verapamil decreases heart rate and slows atrioventricular nodal conduction. These properties make it a good choice for the treatment of supraventricular tachyarrhythmias. Verapamil has a negative intropic effect that can be detrimental in patients with borderline cardiac reserve. Diltiazem also decreases atrioventricular conduction and heart rate but to a lesser extent than verapamil. All dihydropyridine calcium channel blockers can exert a baroreceptor-mediated reflex increase in heart rate because they have potent vasodilating effects. Non-dihydropyridines are less potent vasodilators.[7,10]

Table 3

Calcium Channel Blocker Classification	
Non-dihydropyridines	**Dihydropyridines**
Diltiazem Verapamil	Amlodipine Felodipine Isradipine Nicardipine Nifedipine Nisoldipine

III. Safety

Contraindications
General contraindications of calcium channel blockers include: hypersensitivity to drug or any components, sick sinus syndrome, second or third degree heart block (not in patients with a pacemaker), and patients suffering from hypotension (systolic BP <90 mmHg, for diltiazem and verapamil). Diltiazem is contraindicated in patients with acute MI or those with pulmonary congestion documented by radiography. Nicardipine is contraindicated in patients with advanced aortic stenosis. Verapamil should not be used in patients suffering from severe left ventricular dysfunction, severe heart failure or cardiogenic shock. Also those patients with atrial fibrillation or atrial flutter with an accessory bypass tract are not candidates for therapy with verapamil.[11,13]

Special Precautions of Class
Calcium channel blockers should be used with caution in patients with congestive heart failure (CHF) and impaired hepatic function. Patients should be aware that abrupt withdrawal of these agents can be associated with increased frequency and duration of chest pain. Therefore, these agents should be discontinued via a gradual taper to avoid this potential adverse reaction. Calcium channel blockers are FDA pregnancy category C and verapamil, diltiazem, nifedipine, and nicardipine appear in the breast milk. It is unknown whether isradipine, amlodipine, nisoldipine, or felodipine are excreted in breast milk.[11,13, 61]

Side Effects

Calcium channel blockers are generally well tolerated with mild side effects.   Only a small fraction of patients discontinue these drugs because of perceived adverse drug reactions.[62] Several of the calcium channel blockers are associated with a higher incidence of side effects than the others. Verapamil is associated with more constipation than the other calcium channel blockers. Peripheral edema has been associated with higher doses of dihydropyridine calcium channel blockers. Other side effects (dizziness, flushing, headache) related to vasodilation occur more often with the dihydropyridines. Reflex tachycardia has been associated with the dihydropyridine calcium channel blockers more than the non-dihydropyridine calcium channel blockers. Gingival hyperplasia has been most commonly documented with diltiazem and nifedipine but may occur with any of the calcium channel blockers.[7]

Significant Drug Interactions[11,30,31]
Clinically important drug interactions exist for this class of drugs. Clinically significant drug interactions [rated as 1 (major severity) or 2 (moderate severity) and well documented] for the calcium channel blockers are listed below.

Azole antifungals (nisoldipine)
Antiarrhythmics (verapamil)
Barbiturates (felodipine, nifedipine)
Benzodiazepines (diltiazem)
Beta blockers (verapamil, diltiazem)
Buspirone (diltiazem, verapamil)
Carbamazepine (verapamil, felodipine, diltiazem)
Cimetidine (nifedipine)
Cisapride (nifedipine)
Cyclosporine (verapamil, diltiazem, nicardipine)
Digoxin (verapamil)
Diltiazem (nifedipine)
Erythromycin (felodipine)
Ethanol (verapamil)
Grapefruit Juice (verapamil, felodipine, nifedipine, nisoldipine)
HMG-CoAs Reductase Inhibitors (atorvastatin, lovastatin, simvastatin) (verapamil, diltiazem)
                                          (lovastatin)   (isradipine)
Itraconazole (felodipine)
Methylprednisolone (diltiazem)
Moricizine (diltiazem)
Nondepolarizing Muscle Relaxants
Phenytoin (felodipine, nisoldipine)
Prazosin (verapamil)
Rifampin (nifedipine, verapamil)
Sirolimus (diltiazem)
Tacrolimus (diltiazem, nifedipine)
Theophylline (diltiazem)
Quinidine (verapamil, diltiazem)

IV. Dosing and Administration Considerations

Generic Name	Example Brand Names	Usual Dose in Hypertension[11,13]	Frequency[11,13]
Amlodipine besylate	Norvasc	2.5-10mg	QD
Diltiazem- sustained release	Cardizem SR	60-180mg	BID
Diltiazem- extended release	Cardizem LA	120-540mg	QD
	Cardizem CD	120-360mg	QD
	Dilacor XR	120-540mg	QD
	Tiazac	120-540mg	QD
Felodipine	Plendil	2.5-10mg	QD
Isradipine- immediate release	Dynacirc	2.5-10mg	BID
Isradipine- extended release	Dynacirc CR	5-10mg	QD
Nicardipine- immediate release	Cardene	60-120mg	TID
Nicardipine- extended release	Cardene SR	60-120mg	BID
Nifedipine- extended release	Adalat CC	30-90mg	QD
	Procardia XL	30-90mg	QD
Nisoldipine	Sular	10-60mg	QD
Verapamil- immediate release	Calan	40-160mg	TID
	Verelan	120-480mg	QAM
Verapamil- sustained release	Calan SR	120-480mg	QD-BID
	Isoptin SR	180-480mg	QD
Verapamil-controlled onset- extended release	Covera HS	180-480mg	HS
	Verelan PM	100-400mg	HS

V. Comparative Effectiveness

Dihydropyridine Calcium Channel Blockers and All Cause Mortality
Trials have evaluated the efficacy of treating hypertension in patients with dihydropyridine calcium channel blockers as first line agents and evaluated major cardiovascular disease end points and all-cause mortality. One concern is that not all the trials had adequate power to detect a difference in all cause mortality; most incorporated small numbers of patients and were powered adequately only to detect a difference in cardiovascular events. More importantly, there was a high degree of variation between different anti-hypertensive medications given in the trials making it impossible to determine which anti-hypertensive agent was responsible for the effect.[63-73] (See Table 3 in Appendix A for a summary of the trials.)

Non-dihydropyridine Calcium Channel Blockers and All Cause Mortality
Trials have evaluated the efficacy of treating hypertension in patients with non-dihydropyridine calcium channel blockers as first line agents and evaluated major cardiovascular disease end points and all-cause mortality. Two studies, CONVINCE and NORDIL[74,75] compared a non-dihydropyridine to a diuretic or a

beta blocker and one study compared verapamil to a diuretic.[76] No significant difference was documented in any of the trials. These results do not differ from the dihydropyridines. Indirect comparisons between the dihydropyridines and non-dihydropyridines are difficult and cannot be made. Similar to the trials with dihydropyridine calcium channel blockers, there are important differences in patient populations, interventions and the comparator drugs.[74-76] (See Table 4 in Appendix A for a summary of the trials.)

Head to Head trials of calcium channel blockers
Head to head trials of calcium channel blockers have been performed to compare efficacy of blood pressure control, safety and tolerability. Results generally agree in their comparable efficacy in lowering blood pressure and differ only slightly in side effect profiles.[77-79] (See Appendix A for a summary of trials.)

Guideline Recommendations
American Diabetes Association 2003 Standards of Medical Care for Patients with Diabetes Mellitus
Cardiovascular events associated with lowering of the blood pressure have been found to be reduced with the following classes of drugs, ACE Inhibitors, angiotensin receptor blockers (ARBs), beta blockers, diuretics and calcium channel blockers. Studies suggest that ACE Inhibitors may be superior to dihydropyridine calcium channel blockers in reducing cardiovascular events. In patients with intolerance to ACE Inhibitors or angiotensin receptor blockers (ARBs) with microalbuminuria or overt nephropathy, a non-dihydropyridine calcium channel blocker or beta blocker should be considered.[80]

JNC-7
Clinical trial outcomes data prove that lowering blood pressure with several classes of drugs, including calcium channel blockers, will reduce the complications of hypertension. Compelling indications for using calcium channel blockers in patients with hypertension include high coronary disease risk and diabetes. In addition, evidence exists that in the African American population calcium channel blockers or diuretics may be more effective than monotherapy with beta-blockers, ACE Inhibitors or ARBs. These agents may be useful in patients with Raynaud's syndrome and specific arrhythmias.[3]

2003 WHO/ISH (World Health Organization/International Society of Hypertension Statement on Hypertension
The data regarding the use of calcium channel blockers conclusively demonstrates reduction in both morbidity and mortality. When used as monotherapy, a calcium channel blocker may lower blood pressure in African Americans and older patients more effectively than an ACE Inhibitor or a beta blocker.[35]

2003 ESH/ESC Guidelines for Management of Arterial Hypertension
Calcium channel blockers are suitable for initiation and maintenance of therapy. In trials of isolated systolic hypertension, first-line drugs are comprised of a diuretic or a dihydropyridine calcium-channel blocker. Calcium channel blockers are one of the preferred drug classes in some pregnant women.[36,37]

Management of High Blood Pressure in African Americans Consensus Statement
Calcium channel blockers may have greater blood pressure-lowering efficacy than do other classes in African Americans.[38]

Treatment Guidelines from the Medical Letter
Hypertension should not be treated with short acting calcium channel blockers. In elderly patients with hypertension, dihydropyridine calcium channel blockers (sometimes in combination with other agents) showed a decrease in the incidence of stroke compared to placebo.[9]

VI. Conclusions

Based on this evidence, we are unable to conclude that there is a brand name calcium channel blocker that has a significant clinical advantage in the treatment of hypertension.

All brand products within the class reviewed are comparable to each other and to the generic products in that class and offer no significant clinical advantage over other alternatives in general use.

VII. Recommendations

No brand calcium channel blocker is recommended for preferred status.

Diuretics AHFS Class 402800

This review encompasses all dosage forms and strengths.

I. Indications and Availability

Generic Name	Example Brand Names	Generic Available*[11,12]	FDA Approved Indications[11,13,81-91]
Amiloride	Midamor	Yes	HTN CHF
Bendroflumethiazide	Naturetin-5	Currently only available in combination products.	HTN Edema
Bumetanide	Bumex	Yes	Edema
Chlorthalidone	Thalitone	Yes	HTN Edema
Chlorothiazide	Diuril	Yes	HTN Edema
Ethacrynic acid	Edecrin	No	Edema Short-term management of ascites caused by malignancy, idiopathic edema, or lymphedema. Short-term management of children with CHF or nephritic syndrome.
Furosemide	Lasix	Yes	HTN Edema
Hydrochlorothiazide	Ezide Microzide Oretic	Yes	HTN Edema
Hydroflumethiazide	Diucardin Saluron	Yes	HTN Edema
Indapamide	Lozol	Yes	HTN Edema
Methyclothiazide	Aquatensen Enduron	No Yes	HTN Edema
Metolazone	Mykrox Zaroxolyn	No Yes	HTN HTN Edema
Polythiazide	Renese	No	HTN Edema
Spironolactone	Aldactone	Yes	HTN Primary hyperaldosteronism Hypokalemia Edema
Torsemide	Demadex	Yes	HTN Edema

*Generics available in at least one dosage form or strength.

Inspra (eplerenone) was FDA approved in December 2002 but is not expected to be available commercially until December 2003 and may be reviewed at a future time.

II. Comparative Pharmacology Parameters

Thiazide Diuretics:
Mechanism of action: The exact mechanism of action is unknown. Initially, thiazide diuretics act to increase the excretion of sodium and chloride by inhibiting re-absorption in the ascending loop of Henle and the early distal tubules of the kidney. With chronic use, blood pressure is lowered by the decrease in peripheral vascular resistance.[6,11]

Loop Diuretics:
Mechanism of action: Loop diuretics all have different mechanisms of action, but all act by inhibiting the reabsorption of sodium in the loop of Henle and therefore increasing the excretion of sodium and water. Furosemide, bumetanide, torsemide, and ethacrynic acid exhibit this action by blocking the Na+/K+/Cl-pump. Furosemide and ethacrynic acid have additional actions on the proximal and distal tubules to inhibit the reabsorption of sodium. Bumetanide acts at the proximal tubule to inhibit reabsorption, but not the distal tubule.[11,81]

Potassium Sparing Diuretics:
Mechanism of action: Potassium sparing diuretics act mainly at the distal tubule to inhibit the reabsorption of sodium, thus decreasing the amount of potassium that is lost. Spironolactone competitively inhibits aldosterone in the distal tubules to block sodium reabsorption. Triamterene and amiloride directly inhibit the active transport of sodium and potassium at the distal tubule and collecting ducts.[11,81]

III. Safety

Contraindications
Thiazide diuretics and loop diuretics should be avoided in patients with anuria, hypersensitivity, or severe liver disease. Potassium sparing diuretics should be avoided in patients who have preexisting or drug-induced hyperkalemia.[11,13]

Special Precautions of Class
Thiazide diuretics should be used with extreme caution in pregnancy and lactation, fluid electrolyte balance, severe renal disease, impaired hepatic function or progressive liver disease because they may precipitate hepatic coma[11,13] and should be used in caution in patients with gout.[3] Precautions with **loop diuretics** include: pregnancy and lactation, hepatic cirrhosis and ascites, otoxicity, Systemic Lupus Erythematosus (SLE), diarrhea, diabetes mellitus, renal impairment, and children. **Potassium sparing diuretics** should be used with caution in pregnancy and lactation, hyperkalemia, diabetes mellitus, metabolic or respiratory acidosis, renal or hepatic impairment and children.[11,13]

Significant Side Effects of Diuretic Agents[7,11,13]

Thiazide Diuretics	Loop Diuretics	Potassium Sparing Diuretics
Hypokalemia	Hypokalemia	Hyperkalemia
Hypomagnesemia	Hypomagnesemia	Gynecomastia (spironolactone)
Hypercalcemia	Hypocalcemia	
Hyperuricemia	Hyperuricemia	
Hyperglycemia	Hyperglycemia*	
Hyperlipidemia	Hyperlipidemia *	
Sexual Dysfunction	Sexual Dysfunction	

*Less of an effect than thiazide diuretics

Significant Drug Interactions[11,30, 31]
Clinically important drug interactions exist for this class of drugs. Clinically significant drug interactions [rated as 1 (major severity) or 2 (moderate severity) and well documented] for the diuretics class are listed in the table below.

Thiazide Diuretics	Loop Diuretics	Potassium Sparing Diuretics
Antidiabetic agents Bile acid sequestrants Cisapride Digoxin Lithium Loop diuretics	ACE Inhibitors Aminoglycosides Bile acid sequestrants Cisapride Cisplatin Digoxin Lithium NSAIDS Theophylline Thiazide diuretics Phenytoin	ACE Inhibitors Potassium preparations/supplements

IV. Dosing and Administration Considerations

Generic Name	Example Brand Names	Usual Dose in Hypertension[11,13]	Frequency[11,13]
Amiloride	Midamor	5-10mg	QD
Bendroflumethiazide	Naturetin-5	5-20mg	QD-BID
Bumetanide	Bumex	0.5-2mg	QD
Chlorthalidone	Thalitone	15-50mg	QD
Chlorothiazide	Diuril	250-500mg	QD-BID
Ethacrynic acid	Edecrin	25mg-100mg	QD
Furosemide	Lasix	40mg	BID
Hydrochlorothiazide	Ezide, Oretic, Microzide	12.5-50mg	QD
Hydroflumethiazide	Diucardin, Saluron	12.5-50mg	QD
Indapamide	Lozol	1.25-5mg	QD
Methyclothiazide	Aquatensen, Enduron	2.5-5mg	QD
Metolazone	Mykrox Zaroxolyn	0.5-1.0mg 2.5-5mg	QD QD
Polythiazide	Renese	2-4mg	QD
Spironolactone	Aldactone	25-50mg	QD-BID
Torsemide	Demadex	5-10mg	QD

V. Comparative Effectiveness
Thiazide-type diuretics have been the basis of antihypertensive therapy in most outcome trials. Low-dose diuretics are the most effective first line treatment for preventing occurrence of cardiovascular disease morbidity and mortality.[34]   **Loop diuretics** should be reserved for patients with hypertension who have more significant renal insufficiency.[6]   **Potassium sparing diuretics** can be used to treat patients who develop clinically significant hypokalemia while taking thiazide diuretics.[10]

Guideline Recommendations
JNC-7

Thiazide-type diuretics should be considered as initial therapy for most patients with hypertension, either alone or in combination with another class (ACE Inhibitors, angiotensin II receptor blockers (ARBs), beta blockers, and calcium channel blockers) that have demonstrated benefits in randomized controlled outcome trials. Diuretics can enhance the efficacy of multiple drug regimens and are effective at controlling blood pressure.

Compelling indications for use of a diuretic in hypertension include heart failure, high coronary disease risk, diabetes and recurrent stroke prevention. African American population may be less sensitive to the blood pressure lowering effects of monotherapy with beta blockers, ACE Inhibitors or angiotensin II receptor blockers (ARBs) compared to diuretics or calcium channel blockers.[3]

2003 WHO/ISH (World Health Organization/International Society of Hypertension Statement on Hypertension
The data regarding the use of diuretics conclusively demonstrates reduction in both morbidity and mortality. When used as monotherapy, a diuretic may lower blood pressure in African Americans and older patients more effectively than an ACE Inhibitor or a beta blocker.[35]

2003 ESH/ESC Guidelines for Management of Arterial Hypertension
Diuretics are suitable for initiation and maintenance of therapy. In trials of isolated systolic hypertension, first-line drugs are comprised of a diuretic or a dihydropyridine calcium-channel blocker.[36,37]

Management of High Blood Pressure in African Americans Consensus Statement
Thiazide diuretics and calcium channel blockers may have greater blood pressure-lowering efficacy than other classes in African Americans. All antihypertensive drug classes are effective and associated with blood pressure-lowering in African Americans. However, combination therapy is frequently required to achieve and maintain goal blood pressure. [38]

Treatment Guidelines from the Medical Letter
Thiazide type diuretics have shown decreased mortality in patients with hypertension. Hydrochlorothiazide and chlorthalidone are the most widely used. Doses as low as 6.25 mg are now used to enhance the effectiveness of other drugs while minimizing adverse effects such as hypokalemia, hyperuricemia, hypercholesterolemia and hyperglycemia.[9]

Loop diuretics can be used to treat hypertension in patients with renal insufficiency (CrCl below 30 to 50 ml/min). In treating patients with hypertension, loop diuretics may be less effective than thiazide diuretics in patients without renal insufficiency.[9]

Potassium-sparing diuretics can be used with other diuretics to prevent or correct hypokalemia. These drugs can cause hyperkalemia and it is important that they be used with caution in patients with renal insufficiency and those taking drugs that can increase potassium levels such as ACE Inhibitors or angiotensin II receptor blockers (ARBs).[9]

VI. Conclusions

Overwhelming evidence supports diuretics' beneficial effects in the treatment of hypertension. Because the thiazide class of drugs have the same pharmacologic effects, they are generally interchangeable with the proper dosage adjustment.[92] All thiazide diuretics are equally effective in lowering blood pressure, the major differences are half lives and duration of the diuretic effect.[7]

All brand products within the class reviewed are comparable to each other and to the generics products in that class and offer no significant clinical advantage over other alternatives in general use.

VII. Recommendation

No brand diuretic is recommended for preferred status.

Hypotensive agents AHFS Class 240800

This review encompasses all dosage forms and strengths.

I. Indications and Availability

Generic Name	Example Brand Names	Generic Available*[11,12]	Indications[11,13,93-99]
Clonidine	Catapres	Yes	HTN
Clonidine transdermal	Catapres TTS	No	
Guanabenz	Wytensin (no longer available in brand name, only generic)	Yes	HTN
Guanfacine	Tenex	Yes	HTN
Hydralazine	Apresoline (no longer available in brand name, only generic)	Yes	HTN
Mecamylamine	Inversine	No	HTN
Methyldopa/methyldopate HCL	Aldomet	Yes	HTN
Minoxidil	Loniten	Yes	HTN
Reserpine	Serpasil (no longer available in brand name, only generic)	Yes	HTN

*Generics available in at least one dosage form or strength.

II. Comparative Pharmacology Parameters

Central alpha$_2$-receptor antagonists/Centrally acting drugs
>   Clonidine
>   Guanabenz
>   Guanfacine
>   Methyldopa

Mechanism of action: Inhibit sympathetic outflow to the heart, kidneys and peripheral vasculature by stimulating alpha$_2$ receptors in the central nervous system, which results in peripheral vasodilation.[10]

Peripheral Adrenergic Neuron Antagonists
>   Reserpine

Mechanism of action: Inhibit sympathetic outflow to the heart, kidneys and peripheral vasculature by stimulating alpha$_2$ receptors in the central nervous system, which results in peripheral vasodilation.[10]

Arterial vasodilators
>   Hydralazine
>   Minoxidil

Mechanism of action: Vasodilation by direct relaxation of arteriolar smooth muscle, reducing perfusion pressure, and increasing sympathetic output from the vasomotor center, increasing heart rate, cardiac output and renin release.[10]

Ganglionic Blocker
>   Mecamylamine

Mechanism of action: Inhibits acetylcholine at the autonomic ganglia, causing a decrease in blood pressure.[81]

III. Safety

Contraindications/Precautions/Drug Interactions

Generic Name	Contraindications[94-100,102]	Precautions[94-102]	Clinically Significant Drug Interactions[11,30,31]
Clonidine	• Hypersensitivity to clonidine or adhesive components	• Cerebrovascular disease • Chronic renal failure • Conduction disturbances • Contact dermatitis (topical patch) • Defibrillation or cardioversion (topical patch) • Hemodynamic instability • Myocardial infarction, recent • Obstetric, post-partum, or perioperative pain • Sudden cessation of clonidine treatment	Beta blockers Tri-cyclic Antidepressants
Guanabenz	• Hypersensitivity to guanabenz products	• Avoid abrupt withdrawal (rebound hypertension) • Cerebrovascular disease • Liver disease • Myocardial infarction (recent) • Renal impairment • Sedation • Severe coronary insufficiency	CNS Depressants
Guanfacine	• Hypersensitivity to guanfacine	• Avoid abrupt withdrawal (rebound hypertension) • Cerebrovascular disease • Liver disease • Myocardial infarction (recent) • Renal impairment • Sedation • Severe coronary insufficiency	CNS Depressants
Hydralazine	• Dissecting aortic aneurysm • Hypersensitivity to hydralazine	• History of cerebrovascular disease or stroke • Coronary artery disease • Liver disease • Mitral valve disease • Renal impairment • Systemic lupus erythematosus	Beta blockers (metoprolol, propranolol)

Contraindications/Precautions/Drug Interactions (cont.)

Generic Name	Contraindications[94-100,102]	Precautions[94-102]	Clinically Significant Drug Interactions[11,30,31]
Mecamylamine	• Coronary insufficiency • Glaucoma • Hypersensitivity to mecamylamine • Myocardial infarction, recent • Patients treated with antibiotics and sulfonamides • Pyloric stenosis insufficiency	• Arteriosclerosis • Avoid abrupt withdrawal • Bladder neck obstruction, urethral stricture • Cerebral insufficiency or following a cerebrovascular accident • Gastrointestinal obstruction • Potentiation of hypotensive effects due to excessive heat, fever, infection, hemorrhage, pregnancy, anesthesia, alcohol consumption, salt depletion, or diarrhea • Prostatic hypertrophy	Antibiotics Sulfonamides
Methyldopa	• Current MAOI therapy • Hypersensitivity to methyldopa • Liver disease (with or without previous association with methyldopa therapy)	• Avoid abrupt withdrawal • Congestive heart failure • Dialysis patients (risk of hypertension following procedure) • Edema • Elderly • Hemolytic anemia • Hypotension • Liver disease • Severe bilateral cerebrovascular disease	Sympathomimetics
Minoxidil	• Hypersensitivity to minoxidil products • Pheochromocytoma	• Angina pectoris (exacerbation) • Cerebrovascular disease • Concomitant use of guanethidine (profound orthostatic effects) • Malignant hypertension • May cause congestive heart failure (without adequate diuretic therapy) • Myocardial infarction (recent) • Pericardial effusion, pericarditis • Renal failure or dialysis	No significant drug interactions.
Reserpine	• Active GI disease • Depression • Electroshock therapy • Hypersensitivity to reserpine alkaloids • Severe renal failure • Ulcerative colitis	• Asthma • Elderly • History of gall stones • History of peptic ulceration • History of ulcerative colitis	Sympathomimetics

Side Effects
Central alpha 2-receptor antagonists/centrally acting drugs are not first-line anti-hypertensive agents because they cause more side effects than other agents, including sedation, dry mouth, and with abrupt discontinuation can cause nervousness, palpitations, headache, perspiration, nausea, and agitation. In some cases, sudden discontinuation can cause rebound hypertension to potentially dangerous levels.[10] Higher rates of sexual dysfunction are associated with centrally acting agents.[7] Depression has been often associated with reserpine; however, it appears as though this was dose related and occurred when an excess of 1.0mg daily was used in the 1950's. The problem can be minimized by not exceeding a dose of 0.25mg/day. At low doses, the rate of depression with reserpine is equivalent to that of beta-blockers, diuretics or placebo.[103,104] Reserpine has been used as a second-step agent for many large, landmark studies in hypertension.[73,103] Methyldopa remains one of the preferred agents in pregnant women due to the safety for the fetus.[3]

The arterial vasodilators are effective at decreasing blood pressure. However, efficacy decreases as fluid accumulation occurs, which is the reason patients are often started on a diuretic (to decrease fluid retention) and a beta blocker (to decrease tachycardia.) They are used *infrequently* and have been associated with severe side effects. Hydralazine has been associated with drug induced lupus (reversible upon discontinuation) at a dose as low as 100mg per day, and the risk increases as the dose approaches 200mg. It does have a role in combination with isosorbide dinitrate in patients with heart failure. Oral minoxidil should be only used if a triple drug regimen fails or if other anti-hypertensives are contraindicated. Fluid retention is also a common side effect and could therefore cause or exacerbate heart failure. In high risk patients, minoxidil can precipitate angina. To prevent this it should be administered with a diuretic and a beta blocker. Hypertrichosis occurs in over 80% of patients.[10,105]

IV. Dosing and Administration Considerations

Generic Name	Example Brand Names	Usual Dose in Hypertension[11,13]	Frequency[11,13]
Clonidine	Catapres	0.1-0.3mg	BID-TID
Clonidine transdermal	Catapres TTS	0.1-0.3mg/day	1 patch per week
Guanabenz	Wytensin (no longer available in brand name, only generic)	4-64mg	BID
Guanfacine	Tenex	1-3mg	HS
Hydralazine	Apresoline (no longer available in brand name, only generic)	40-200mg	BID-QID
Mecamylamine	Inversine	2.5-25mg	QD-TID
Methyldopa/methyldopate HCL	Aldomet	250-2000mg	BID-QID
Minoxidil	Loniten	5-40mg	QD-BID
Reserpine	Serpasil (no longer available in brand name, only generic)	0.05-0.1mg	QD

V. Comparative Effectiveness

These agents are generally accepted to be effective anti-hypertensive agent, despite absence of outcome data. Agents such as clonidine, reserpine, hydralazine and minoxidil have been used as add-on therapy, if needed, to control blood pressure, in landmark clinical trials.[71,73,103]

Guideline Recommendations
JNC-7
These agents are not recommended as initial agents for treatment of uncomplicated hypertension or as therapy for compelling indications. Methyldopa is one of the preferred agents in pregnant women due to the safety of the mother and the fetus.[3]

2003 WHO/ISH (World Health Organization/International Society of Hypertension Statement on Hypertension
Central alpha 2-receptor antagonists (e.g. clonidine) or peripheral adrenergic neuron antagonists (e.g. reserpine) may be used in some cases despite the absence of outcome data.[35]

2003 ESH/ESC Guidelines for Management of Arterial Hypertension
These agents are not recommended as initial agents for treatment of hypertension. The role for these agents is stated as follows: these agents may be used in combination with first line therapies (diuretics, ACE Inhibitors, angiotensin II receptor blockers or beta blockers) if necessary, as three or four drugs may be required to control blood pressure. Methyldopa is a drug of choice in pregnancy.[36,37]

Management of High Blood Pressure in African Americans Consensus Statement
These agents are not addressed in the consensus statement.[38]

Treatment Guidelines from the Medical Letter
Clonidine, guanabenz, guanfacine and methyldopa frequently cause sedation, dry mouth and impotence. Hydralazine and minoxidil often produce reflex tachycardia, but rarely orthostatic hypotension. These agents should be avoided in coronary disease. The hydralazine maintenance dose should be limited to 200mg/day to decrease the likelihood of a lupus-like reaction. Minoxidil is potent in its blood pressure lowering capability; however, it should be reserved for severe hypertension only due to its potentially severe side effects of severe fluid retention and hirsutism. Reserpine is an effective antihypertensive, but in higher than recommended doses, it can cause severe depression. Hypotension is common with this agent and is exacerbated by vasodilatation cause by heat, exercise or alcohol.[9]

VI. Conclusion

All brand products within the class reviewed are comparable to each other and to the generic and OTC products in that class and offer no significant clinical advantage over other alternatives in general use.

Mecamylamine and minoxidil possess an extensive adverse effect profile compared to the other brand or generic products in the hypotensive class.

VII. Recommendation

No brand hypotensive agent is recommended for preferred status.

No brand name version of mecamylamine should be placed in preferred status regardless of cost.
No brand name version of minoxidil should be placed in preferred status regardless of cost.

Hypotensive Combination Agents AHFS Class 240800
This review encompasses all dosage forms and strengths.

I. Indications and Availability

Generic Name	Example Brand Names[11,13,81]	Indications[11,13,102]
Bendroflumethiazide / rauwolfia serpentina	Flumezide	HTN
Chlorothiazide / methyldopa	Aldoclor	HTN
Chlorthalidone / clonidine HCl	Clorpres, Combipres	HTN
Hydrochlororthiazide / deserpidine	Oreticyl	HTN
Hydrochlororthiazide / hydralazine	Hydra-Zide	HTN CHF
Hydrochlorothiazide / reserpine	Hydro-Reserp	HTN
Hydrochlororthiazide / methyldopa	Aldoril , Aldoril D	HTN
Hydrochlororthiazide / hydralazine HCl / reserpine	Camp-Ap-Es, Uni-Serp, Serpazide	HTN
Hydroflumethiazide / reserpine	Salutensin, Salutensin-Demi	HTN
Methyclothiazide / deserpidine	Enduronyl, Enduronyl Forte	HTN

II. Comparative Pharmacology Parameters

Combination agents would be expected to exhibit a pharmacology/pharmacokinetics profile that is similar to both the agents in the product. (See review on diuretics and hypotensive agents).

III. Safety

Combination agents would be expected to exhibit an adverse effects profile that is similar to both the agents in the product. (See review on diuretics and hypotensive agents).

IV. Dosing and Administration Considerations

Hypotensive combinations consisting of a hypotensive agent and a thiazide diuretic are not recommended as initial therapy for hypertension. Dosage should be adjusted by administering and titrating the dosage of each drug separately. If the optimum maintenance dose is determined and a commercial product is available in that fixed dose, then a product may be used. However, whenever dosage adjustment is necessary, the drugs should be administered separately.[13]

V. Comparative Effectiveness

Guideline Recommendations
JNC- 7
When blood pressure is more than 20/10mmHg above an individual's goal blood pressure then consideration of multi drug therapy should occur. Multi drug therapy consists of two drugs either as separate prescriptions or in fixed-dose combinations.[3]

2003 WHO/ISH (World Health Organization/International Society of Hypertension Statement on Hypertension
These agents are not directly addressed in the statement.[35]

Management of High Blood Pressure in African Americans Consensus Statement
These agents are not addressed in the consensus statement.[36-37]

2003 ESH/ESC Guidelines for Management of Arterial Hypertension
These agents are not recommended as initial agents for treatment of hypertension. The role for these agents is stated as follows: these agents may be used in combination with first line therapies (diuretics, ACE Inhibitors, angiotensin II receptor blockers or beta blockers) if necessary, as three or four drugs may be required to control blood pressure.[38]

Treatment Guidelines from the Medical Letter
These agents are not addressed in this guideline.[9]

VI. Conclusion

It is recommended that these agents should not be first line or initial therapy in the management of hypertensive patients. The current lack of evidence that one or more agents have a significant clinical advantage and the availability of numerous generic products, a brand name product is not recommended for preferred status for the hypotensive combination agent class.

All brand products within the class reviewed are comparable to each other and to the generic products in that class and offer no significant clinical advantage over other alternatives in general use.

VII. Recommendation

No brand hypotensive combination product is recommended for preferred status.

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Appendix A
Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).
JAMA. 2002 Dec 18;288(23):2981-97.

Study Design: Randomized, double blind, active controlled trial.

Objective: To determine whether treatment with a calcium channel blocker or an ACE Inhibitor lowers the incidence of coronary heart disease (CHD) or other cardiovascular disease (CVD) events vs. treatment with a diuretic.

Participants and Setting: The 33, 357 participants in 623 North American Centers were age 55 years or older with hypertension and at least one other CHD risk factor.

Interventions: Participants were randomly assigned to receive step 1 therapy consisting of: chlorthalidone, 12.5 to 25mg daily (n=15,255); amlodipine, 2.5 to 10mg daily (n=9,048); or lisinopril, 10to 40 mg daily (n=9054) for a planned follow-up of approximately 4 to 8 years. If this therapy did not control blood pressure to the goal of less than 140/90 step 2 therapy was initiated at the discretion of the health care provider (atenolol 25-100mg daily, reserpine 0.05 – 0.2 mg daily or clonidine 0.1-0.3 mg daily. Step 3 therapy was hydralazine 25-100mg twice daily, if necessary. In addition, other drugs including the low doses of the drugs in step 1 were allowed if clinically indicated.

Outcome Measures: The primary outcome was combined fatal CHD or non fatal myocardial infarction, analyzed by intention-to-treat analysis. Secondary outcomes were all-cause mortality, stroke, combined CHD (primary outcomes, coronary revascularization, or angina with hospitalization), and combined CVD (combined CHD, stroke, treated angina without hospitalization, heart failure (HF) and peripheral arterial disease.

Participant characteristics: Baseline characteristics were well matched for age (mean age was 67 years), race (47% were Caucasian) and sex (47% were female). Baseline mean systolic blood pressure (SBP)/diastolic blood pressure (DBP) was 146/84, at baseline 90.2% of participants were receiving anti-hypertensive therapy, and .

Mean Follow-up: 4.9 years

Results: The primary outcome (combined fatal CHD or non-fatal myocardial infarction) occurred in 2,956 participants, with no difference between the three treatments in the incidence of the primary endpoint. The 6 year rate per 100 persons was: 11.5, 11.3 and 11.4 for chlorthalidone, amlodipine and lisinopril respectively. In addition, all cause mortality did not differ between groups.

Other results:

	chlorthalidone (%)	amlodipine (%)	lisinopril (%)
Participants receiving original study drug	80.5	80.4	72.6
Participants receiving step 2 therapies	40.7	39.5	43
Participants achieving goal blood pressure of less than 140/90	68	66	61

Conclusion: The investigators concluded that thiazide-type diuretics are superior in preventing 1 or more major forms of CVD and should be preferred as first-line anti-hypertensives.

Discussion: ALLHAT investigators mentioned that the results apply directly to the study drugs. They further concluded that combined with evidence from other trials, the findings broadly apply to the drug classes (or sub classes in the case of the dihydropyridine calcium channel blockers) that the study drugs represent.[105]

Appendix A

Table 1. Pharmacokinetics of Calcium Channel Blockers[11, 38-54]:

Parameters		Amlodipine	Diltiazem	Felodipine	Isradipine	Nicardipine	Nifedipine	Nisoldipine	Verapamil
Pharmacokinetics	Absolute bioavailability (oral)(%)	64-90	40	≅20	15-24	≅35	45-75 (IR) 84-89 (ER)	≅5	20-35 (IR)
	Peak Plasma Time (hours)	6-12	2-4 (IR) 10-14 (ER) 6-11 (SR)	2.5-5	1.5 (IR) 7-18 (CR)	0.5-2 (IR) 1-4 (SR)	0.5 (IR) 6 (ER)	6-12	1-2 (IR) ≅11 (ER) ≅7-9(SR)
	Protein binding (%)	93	70-80	> 99	95	> 95	92-98	> 99	≅90
	Metabolism	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic
	Half-life, elimination (hours)	30-50	3-4.5 (IR) 4-9.5 (ER) 5-7 (SR)	11-16	8	2-4	≅2 (IR) ≅7 (ER)	7-12	2.8-7.4[1] 4.5-12[2] ≅12 (SR)
	Duration of Action (hours)	24	nd	16-24	8-16	2-6	24	>24	nd
ECG Changes	Heart rate	±	0-↓	↑↑	↑	↑↑	0-↑	±	±
Hemodynamics	Myocardial contractility	0-↓	0-↓	0-↓	↓	0-↓	0-↓	0-↓	↓↓
	Cardiac output/index	↑	0-↑	nd	↑	↑↑	↑	nd	±
	Peripheral vascular resistance	↓↓	↓↓[3]	↓↓[3]	↓↓	↓↓↓	↓↓↓	↓↓[3]	↓↓

↑↑↑ or ↓↓↓= pronounced effect; ↑↑or ↓↓= moderate effect; ↑or ↓= slight effect; ±=negligible amount or effect; **nd** = no data
[1]After single doses.
[2]After repetitive doses.
[3]Dose-related.

Table 2. Pharmacokinetics of Calcium Channel Blockers (cont.) [11, 38-54]:

Parameters		Amlodipine	Diltiazem	Felodipine	Isradipine	Nicardipine	Nifedipine	Nisoldipine	Verapamil
ECG Changes	Heart rate	±	**0-↓**	↑↑	↑	↑↑	**0-↑**	±	±
Hemodynamics	Myocardial contractility	**0-↓**	**0-↓**	**0-↓**	↓	**0-↓**	**0-↓**	**0-↓**	↓↓
	Cardiac output/index	↑	**0-↑**	**nd**	↑	↑↑	↑	**nd**	±
	Peripheral vascular resistance	↓↓	↓↓[3]	↓↓[3]	↓↓	↓↓↓	↓↓↓	↓↓[3]	↓↓

↑↑↑ or ↓↓↓= pronounced effect; ↑↑or ↓↓= moderate effect; ↑or ↓= slight effect; ± =negligible amount or effect; **nd** = no data
[1]After single doses.
[2]After repetitive doses.
[3]Dose-related.

Dihydropyridine Calcium Channel Blocker Trials and the Occurrence of Cardiovascular Morbidity and Mortality									
				Number of Subjects					
Trial	# of pts	Mean Follow-up (years)	Intervention	CHD	Stroke	CHF	Major CV Events	Total Mortality	CV Mortality
MIDAS, 1996[62]	442	3.0	Isradipine	6	6	2	25	8	NA
	441		Diuretics	5	3	0	14	9	NA
ABCD, 1998 & 2000[63,64]	235	5.0	Nisoldipine	27	11	8	47	18	11
	235		ACE-Inhibitor	9	7	10	29	14	6
FACET, 1998[65]	191	2.5	Amlodipine	13	10	0	23	5	NA
	189		ACE-Inhibitor	10	4	0	14	4	NA
NICSEH, 1999[66]	204	4.2	Nicardipine	2	8	0	11	2	2
	210		Diuretics	2	8	3	12	2	0
STOP-2, 1999[67]	2196	5.0	Felodipine/isradipine	179	207	186	450	362	212
	2213		BB or diuretics	54	237	177	460	369	221
	2205		ACE-Inhibitor	139	215	149	437	380	226
INSIGHT, 2000[68]	3157	3.5	Nifedipine	77	67	26	200	153	60
	3164		Diuretic	61	74	12	182	152	52
AASK, 2001 & 2002[69-70]	436	3.0	ACE-Inhibitor	NA	NA	NA	0.59*	18	NA
	217		Amlodipine	NA	NA	NA	1.00*	13	NA
	441		BB (metoprolol)	NA	NA	NA	0.52*	NA	NA
Lewis et al., 2001[71]	579	2.6	ARB	NA	NA	NA	138	87	NA
	567		Amlodipine	NA	NA	NA	128	83	NA
	569		Placebo	NA	NA	NA	144	93	NA
ALLHAT, 2002[72]	15255	4.9	Diuretic	1362	675	870	3941	2203	992
	9048		Amlodipine	798	377	706	2432	1256	592
	9054		ACE-Inhibitor	796	457	612	2514	1314	609

*Indicates relative risk

**SYST-EUR, 1997 & 1999 and ELSA, 2002 were not included in the review because they studied calcium channel blockers (nitrendipine and lacidipine) that are not available commercially in the United States.

Adapted from Psaty BM, Lumley T, Furberg CD, Schellenbaum G, Pahor M, Alderman MH, Weiss NS. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. JAMA. 2003 May 21;289(19):2534-44.

Head to Head trials of dihydropyridine calcium channel blockers

A multi-center, double blind, randomized trial in 161 participants to evaluate the efficacy and tolerability of nisoldipine extended release (dosed 10-40mg) versus Amlodipine (dosed 2.5mg-10mg). The primary outcome was comparison of change from baseline diastolic blood pressures from baseline to week 8. The reductions in systolic blood pressure/diastolic blood pressure for nisoldipine and Amlodipine were -11.7/-9.3 and -14.3/-12.0 respectively. In summary, nisoldipine and amlodipine provide clinically equivalent antihypertensive efficacy.[76]

The second study compared the efficacy and safety of nisoldipine ER and amlodipine in 120 participants in a 6 week multi-center, randomized, double-blind, double-dummy, parallel group study in participants with stage 1 or 2 systemic hypertension and chronic stable angina. Participants were randomized to either nisoldipine ER (dosed 20-40mg) or amlodipine (dosed 5-10mg) once daily and titrate every 2 weeks to achieve a diastolic BP of <90mmHg. At the end of 6 weeks the mean reduction in systolic/diastolic BP from baseline was 15/13 mmHg with nisoldipine ER and 13/11 mmHg with amlodipine (no statistically significant difference). Diastolic BP goals of < 90mm Hg were obtained in 87% of the participants on nisoldipine and 78% of participants on amlodipine. Adverse events were infrequent, and were most commonly associated with vasodilator-related effects (headache and peripheral edema) that occurred with a higher incidence in the nisoldipine ER group. It was concluded the nisoldipine ER and amlodipine provided comparable antihypertensive and anti-ischemic efficacy and both were well tolerated.[77]

In 2003, a randomized, controlled, open label, twelve week trial compared once-daily nifedipine GITS to once-daily amlodipine in participants for the treatment of mild-to-moderate hypertension. One hundred fifty-five participants with essential hypertension (diastolic blood pressure of 95-109) were treated with step 1 therapy consisting of either 30mg nifedipine GITS (n=76) or 5 mg amlodipine (n=79). If the blood pressure was not below 140/90 mmHg after 6 weeks, the dose was increased (step 2) to 60mg once daily in the nifedipine group or 10mg once daily in the amlodipine group. The main outcome parameter was diastolic blood pressure at trough after 12 weeks of therapy. After 12 weeks of therapy the mean diastolic blood pressure was 83.1 and 81.9 mmHg, in the nifedipine and amlodipine groups respectively (p=0.436). No statistically significant difference was detected in the efficacy parameters. Both drugs were well tolerated. The overall incidence of adverse events was 7.9% in the nifedipine group and 10.1% in the amlodipine group. It was concluded that nifedipine in GITS formation and amlodipine are comparably safe and effective treatment options in participants with mild-to-moderate essential hypertension.[78]

Table 4

Trial	# of pts	Mean Follow-up (years)	Intervention	CHD	Stroke	CHF	Major CV Events	Total Mortality	CV Mortality
Non-Dihydropyridine Calcium Channel Blocker Trials and the Occurrence of Cardiovascular Morbidity and Mortality									
				Number of Subjects					
VHAS, 1997[73]	707 707	2.0	Verapamil Diuretics	8 9	5 4	2 0	15 13	5 4	5 4
NORDIL, 2000[74]	5410 5471	4.5	Diltiazem BB or Diuretics	183 157	159 196	63 53	466 453	231 228	131 115
CONVINCE, 2002[75]	8179 8297	3.0	Verapamil BB or Diuretics	133 166	133 118	126 100	364 365	NA NA	152 143

Chart adapted from Psaty BM, Lumley T, Furberg CD, Schellenbaum G, Pahor M, Alderman MH, Weiss NS. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. JAMA. 2003 May 21;289(19):2534-44.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee
Pharmacotherapy Reviews

Section III Table of Contents

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Reviews
Rapid Onset, Long Duration Stimulant Agents for ADHD, AHFS Class 282000 and
Miscellaneous Central Nervous System Agent Indicated for ADHD, Atomoxetine
AHFS Class 289200

I.   **Overview**

Attention Deficit Hyperactivity Disorder (ADHD) is a severe, debilitating disorder that can affect both children and adults. A recent epidemiologic survey reported the prevalence of ADHD in American children at 6.3%,[1] but other sources report the prevalence as high as 12% in school age children, with 60 to 80% of patients continuing to suffer into adolescence or even adulthood.[2] Untreated or under-treated ADHD is associated with adverse sequelae that include delinquent behavior, antisocial personality traits, substance abuse, and other comorbidities.[3] Suboptimal academic performance is often the impetus for initial screening, diagnosis, and subsequent drug therapy.

Stimulant drugs were introduced for the treatment of children with inattention and hyperactivity 65 years ago.[4] There is a plethora of evidence to demonstrate both benefits and risks of stimulant therapy for ADHD; levels of evidence will be discussed later in this review, and are summarized in at least two evidence based clinical practice guidelines.[2,3]

In addition, atomoxetine is a newly approved, non-controlled drug therapy that is indicated for ADHD treatment. There is some evidence to support efficacy for ADHD treatment in both children and adults and this will be covered later in this review.

This review encompasses all dosage forms and strengths.

Rapid Onset, Long Duration Stimulant Agents for ADHD, AHFS Class 282000

Table 1: Dosage Forms

Generic Name	Brand Name Examples	Dosage Form
Mixed Amphetamine Salts	Adderall XR	Capsule
Methylphenidate HCL, extended release	Concerta	Tablet
	Metadate-CD	Capsule
	Ritalin LA	Capsule

II.   **Current Treatment Guidelines and Pharmacology**

Mixed Amphetamine Salts and Methylphenidate
Mixed amphetamine salts and methylphenidate are central nervous system stimulants; although the mechanism of action for ADHD treatment has not been fully elucidated, several theories have been proposed. Sympathomimetic amines facilitate the release of biogenic amines from nerve terminals in the central nervous system.[5] Dopamine concentrations are increased in the mesolimbic system, as are serotonin and norepinephrine in the prefrontal cortex.[5,6]

Mixed amphetamine salts (eg, Adderall; Adderall XR) are more potent sympathomimetic amines versus methylphenidate. Methylphenidate binds to the dopamine transporter in the presynaptic cell membrane, blocking reuptake of dopamine and causing a resultant increase in extracellular dopamine levels.[6] Thus, the piperidine derivative, methylphenidate, is considered a mild CNS sympathomimetic agent. Although both agents are Class II controlled drugs, indicating a significant abuse potential, recent data suggest that oral methylphenidate has a lower potential for abuse.[7] According to evidence based clinical practice guidelines as well as recent meta-analysis,[2,3,8,9] there is no evidence to suggest that drug abuse results from properly

monitored prescribed stimulants.[8,9] The guidelines state that although the abuse of methylphenidate is rare, caution may be indicated in the presence of conduct disorder, preexisting chemical dependency, or a chaotic family. According to the Medical Letter of Drugs and Therapeutics, February 2003 issue as well as other sources cited, if the risk of drug abuse by the patient or the patient's peers or family is high, a non-stimulant medication may be preferable to methylphenidate or mixed amphetamine salts.[8,9]

Several clinical practice guidelines exist that outline the treatment of ADHD. Some guidelines are primarily consensus-based documents (i.e., The Texas Children's Medication Algorithm Project: 2000), whereas others are based on evidence-based medicine and consensus (i.e., The American Academy of Child and Adolescent Psychiatry: 2002[2], and The American Academy of Pediatrics (AAP) Committee on Quality Improvement: 2001[3]). All three guidelines have been reviewed; however, little differences exist between the documents. The American Academy of Pediatrics is the most evidence-based, rigorous, and externally peer reviewed of the three guidelines consulted, since a selected a subcommittee composed of primary care and developmental-behavioral pediatricians and other experts in the fields of neurology, psychology, child psychiatry, education, family practice, and epidemiology. The subcommittee partnered with the Agency for Health-care Quality and Research, as well as the Evidence-based Practice Center at McMaster University, Ontario, Canada to develop the evidence base of literature regarding the treatment of Attention Deficit Hyperactivity Disorder. The resulting systematic review, along with other major studies in this area, was used to formulate recommendations for treatment of children with ADHD. Subcommittee decisions were made by consensus where definitive evidence was not available. The subcommittee report underwent extensive review by sections and committees of the AAP as well as by numerous external organizations before approval from the AAP Board of Directors. It was extensively peer reviewed prior to publication and dissemination.

A summary of the AAP evidence-based guideline (2001) follows:[2]

Once [the ADHD] diagnosis is confirmed, and an interdisciplinary plan of action is established, the clinician should recommend stimulant medication and/or behavior therapy as appropriate to improve outcomes in children with ADHD. When the drug and non-drug therapy has not met target outcomes, clinicians should evaluate the original diagnosis, use of all appropriate treatments, adherence to the treatment plan, and presence of coexisting conditions. Since the core symptoms of ADHD (i.e., inattention, impulsivity, hyperactivity) result in multiple areas of dysfunction relating to a child's performance at home, school, and in the community, the primary goal of treatment is to maximize function. Desired results include:

- Improvements in relationships with parents, siblings, teachers, and peers
- Decreased disruptive behaviors
- Improved academic performance, particularly in volume of work, efficiency, completion, and accuracy
- Increased independence in self-care or homework
- Improved self-esteem
- Enhanced safety in the community, such as in crossing streets or riding bicycles.

Target outcomes should follow from the key symptoms the child manifests and the specific impairments these symptoms cause.

The clinician should recommend stimulant medication (strength of evidence: good) and/or behavior therapy (strength of evidence: fair), as appropriate, to improve target outcomes in children with ADHD (strength of recommendation: strong). The clinician should develop a comprehensive management plan focused on the target outcomes. For most children, stimulant medication is highly effective in the management of the core symptoms of ADHD. For many children, behavioral interventions are valuable as primary treatment or as an adjunct in the management of ADHD, based on the nature of coexisting conditions, specific target outcomes, and family circumstances.

Many studies have documented the efficacy of stimulants in reducing the core symptoms of ADHD. In many cases, stimulant medication also improves the child's ability to follow rules and decreases emotional over-reactivity, thereby leading to improved relationships with peers and parents. Most studies of stimulants have been short-term, demonstrating efficacy over several days or weeks. The MTA study extends the demonstrated efficacy to 14 months. In that study, 579 children 7 to 9.9 years of age with ADHD were randomized to 4 treatment groups: medication management alone, medication and behavior management, behavior management alone, and a standard community care group. The medication management groups followed specific protocols and algorithms in distinction to routine community practice based on clinicians' best judgments. School-aged children with ADHD showed a marked reduction in core ADHD symptoms over a 14-month period when they were treated with medication management alone or a combination of medication and behavior management. Eighty-five percent of the children treated with medication received a stimulant medication. Despite the efficacy of stimulant medications in improving behaviors, many children who receive them do not demonstrate fully normal behavior (e.g., only 38% of medically managed children in the MTA study received scores in the normal range at 1-year follow-up). Although the MTA study demonstrated that efficacy of stimulants lasts at least to 14 months, the longer term effects of stimulants remain unclear, attributable in part to methodological difficulties in other studies.[2]

Stimulant medications currently available include short-, intermediate-, and long-acting methylphenidate, and short-, intermediate-, and long-acting dextroamphetamine. The latter 2 formulations are mixed amphetamine salts (75% dextroamphetamine and 25% levoamphetamine. The McMaster report reviewed 22 studies and showed no differences comparing methylphenidate with dextroamphetamine or among different forms of these stimulants. Each stimulant improved core symptoms equally. Individual children, however, may respond to one of the stimulants but not to another.

At least 80% of children will respond to one of the stimulants if they are tried in a systematic way.[2] Children who fail to show positive effects or who experience intolerable side effects on one stimulant medication should be tried on another of the recommended stimulant medications. The reasons for this recommendation include the following:[2]

- Most children who fail to respond to one medication will have a positive response to an alternative stimulant
- Safety and efficacy of stimulants in the treatment of ADHD compared with nonstimulant medications has not been established
- Numerous crossover trials that indicate the efficacy of different stimulants in the same child
- Idiosyncratic responses to medication

Children who fail 2 stimulant medications can be tried on a third type or formulation of stimulant medication for the same reason. When the selected management for a child with ADHD has not met target outcomes, clinicians should evaluate the original diagnosis, use of all appropriate treatments, adherence to the treatment plan, and presence of coexisting conditions (strength of evidence: weak; strength of recommendation: strong). The clinician should periodically provide a systematic follow-up for the child with ADHD. Monitoring should be directed to target outcomes and adverse effects by obtaining specific information from parents, teachers, and the child (strength of evidence: fair; strength of recommendation: strong). The controlled drug status of both methylphenidate and mixed amphetamine salts ensures follow-up on a monthly basis, since C-II prescriptions cannot have refills; a new prescription is required on a monthly basis.[2]

III.   **Comparative Indications**[10]

Methylphenidate Extended Release Dosage Forms (Concerta, Metadate CD, Ritalin LA)
Methylphenidate is approved for the treatment of ADHD in adults and children greater than 6 years-of-age. Methylphenidate is approved for the treatment of narcolepsy in adults and children greater than 6 years-of-age.

Mixed Amphetamine Salts, extended release (Adderall XR)
Adderall XR® is approved for the treatment of ADHD in adults and children greater than 6 years-of-age.
Adderall XR® is approved for the treatment of narcolepsy in adults and children greater than 6 years-of-age.

Contraindications for *Metadate CD, Ritalin LA, and Concerta*
Patients with anxiety and agitation are not candidates for methylphenidate therapy, nor are patients with glaucoma, motor tics, Tourette's syndrome, or a family history of Tourette's syndrome or seizures.[10]

Contraindications for Adderall XR
Patients with advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, or glaucoma cannot take amphetamines. In addition, patients with psychological agitated states, or a history of drug abuse cannot take amphetamines. During or within 14 days following the administration of monoamine oxidase inhibitors, amphetamines are contraindicated due to the potential for hypertensive crisis.[10]

IV.   Comparative Pharmacokinetic Parameters

Methylphenidate extended release products
Metadate CD
Bioavailability, including Cmax and Area-under-the-Curve (AUC) are not significantly affected when sprinkled on a small amount of applesauce. When Metadate CD is taken with a high fat meal, the first peak is delayed by 1 hour, Cmax is increased by 30%, and AUC is increased by 17%.[10]

Metadate CD and Concerta
The rate and extent of absorption of Metadate CD 20 mg capsule and the Concerta 18 mg tablet were compared in a single dose, randomized, two-way crossover study in 36 adults. The data was normalized for the overall difference in dosage (2 mg); the rate and extent of absorption differed between the two products. Both formulations exhibited biphasic plasma concentration-time profiles and were equivalent in terms of total exposure (AUC_{Total}). However, early exposure (AUC_{0-4} and AUC_{0-6}), the first maximum measured plasma concentration (C_{max-1}), and early plasma MPH concentrations (1.5, 3 and 4 hours) were greater with the capsule formulation, while later plasma MPH concentrations (8, 10 and 12 hours) were greater with the tablet formulation (the Confidence Intervals were outside the $80 – 125\%$ required for equivalence and $p < 0.001$ for all). Similar results were obtained whether or not the data were normalized for the difference in total dose. Based upon these results, the authors concluded the two formulations were not bioequivalent.[12] However, there are a few important facts about the data analysis that are worth noting. Total bioavailability did not differ between the two formulations. Also, 90% confidence intervals versus 95% confidence intervals were used to compare Cmax and AUC at various time points between the two formulations. This increases the chance of making a type 1 error to 10%; normally 95% confidence intervals are used to minimize the chance that a non-significant or erroneous difference is detected that in fact does not exist.

Ritalin LA and Concerta
The rate of absorption differed between Ritalin LA 20 mg capsules and Concerta 18 mg tablets, although the overall AUC between the two formulations were similar. Ritalin LA reached peak plasma concentrations at 2 hours versus Concerta peak plasma concentrations at 6 hours.[13]

Adderall XR
Adderall XR 20 mg has been shown to be bioequivalent to Adderall 10 mg administered twice daily. The AUC of the extended release formulation was not significantly affected by food; however, time to peak plasma concentrations is extended by 2.5 hours (from 5.2 to 7.7 hours) when taken with a high fat meal.[14]

Table 2: Pharmacokinetic Parameters[10-16]

DRUG	ONSET (hours)	DURATION (hours)	Tmax (hours)	ELIMINATION HALF-LIFE (hours)
Adderall XR	1-2	10-12	6-8	12
Concerta	1-2	12-14	6-8	4
Metadate CD	1-2	9	1.5/4.5 (Biphasic)	4
Ritalin LA	1-2	9	2/6.5 (Biphasic)	4

V.   Drug Interactions[19,20]

Methylphenidate XR Products
Carbamazepine: The methylphenidate dose may need to be increased over time to compensate for the hepatic metabolic induction.
Tricyclic antidepressants: Metabolism may be inhibited by methylphenidate, so the dose may need to be decreased.

Adderall XR
Acidifying agents: May decrease amphetamine absorption.
Alkalinizing agents: May increase amphetamine absorption.
Haloperidol: Blocks dopamine receptors in the central nervous system, thereby blocking amphetamine's effect in the CNS.
Tricyclic antidepressants: Amphetamines may interfere with metabolism, thus the TCA dose may be decreased if necessary.
Monoamine oxidase inhibitors (MAOI): Another metabolic interaction occurs with MAOI, decreasing amphetamine concentrations to increase toxicity risk.

VI.   Comparative Adverse Effects

Methylphenidate Extended Release Dosage Forms
The most common adverse effects associated with all extended release methylphenidate products include headache, abdominal pain, anorexia, and insomnia. Rash, pruritus, abdominal pain, and headache were the most common reasons for drug discontinuation in clinical trials.[10] A long term outcomes trial found an eight percent cumulative incidence of new onset tics associated with Concerta.[10] However, a more recent randomized, double blind, placebo controlled, multicenter trial suggests that methylphenidate treated patients with chronic tics and ADHD comorbidity actually had a decrease in tic symptoms at average methylphenidate doses. Doses greater than 40 mg per day were associated with slightly lower actual versus predicted patient heights.[17,18]

Adderall XR
At typical therapeutic doses, the most common adverse effects are anorexia, insomnia, weight loss, emotional liability, and depression. Toxic symptoms include restlessness, tremor, confusion, panic, and hallucinations, but coma and death can occur at toxic doses.[10]

Monitoring parameters include: Patients with hypertension, especially at the start of therapy, and with subsequent dose increases since CNS sympathomimetics can increase blood pressure. Patients with psychosis-type symptoms should avoid CNS sympathomimetics since psychotic symptoms may worsen. Monitor patients with validated 18 item ADHD symptom score to assess efficacy over time. Monitor patients for the most common and the most severe adverse effects that were noted in clinical trials. If a paradoxical aggravation of any symptom occurs, the stimulant dose should be decreased or discontinued.[1,4,9]

VII.   Dosing and Administration

Concerta
The recommended starting dose of Concerta for new patients is 18 mg once daily in the morning. Dosage may be adjusted weekly in 18 mg increments to a maximum of 54 mg per day. Patients converting from immediate- release or sustained-release methylphenidate may follow the dosage conversion chart included in the official labeling.[10]

Metadate CD
The typical starting dose for Metadate CD is 20 mg per day. It may be titrated to a maximum of 60 mg per day, and is available as a 10 mg, 20 mg, and 30 mg capsule. Metadate CD may be swallowed whole with water or other liquid, or the capsule may be opened and sprinkled onto a tablespoonful of applesauce and given immediately. Drinking some fluids, e.g. water, should follow the intake of the sprinkles with applesauce. The capsules and the capsule contents must not be crushed or chewed.[10]

Ritalin LA
The recommended starting dose for Ritalin LA is 20 milligrams daily, with gradual upward titration based on efficacy and tolerability, in weekly 10-mg increments to a maximum of 60 mg daily.[10] Dose conversions from immediate release or other extended release products are included in the package insert.

Adderall XR
The recommended starting dose for Adderall XR in newly diagnosed patients and in those patients switching from another medication is 10 mg. Doses may be increased by 5-10 mg per week up to 30 mg per day. Patients taking the immediate release twice daily form can be switched to an equivalent daily dose of the XR form.[10]

VIII.   Comparative Effectiveness

Ritalin LA, Concerta, Metadate CD, and Adderall XR have all demonstrated efficacy for lowering ADHD symptom scores versus placebo (See appendix).[21-29] Concerta was the first extended release methylphenidate product dosage form designed to last 12 hours.[22-25] Wolrich and Pelham examined potential efficacy differences between once daily Concerta and methylphenidate immediate release three times daily. The results of both studies suggest that the Conner's Global Improvement index is similar between the three times daily and once daily regimens, and that both regimens have greater efficacy versus placebo. However, methodological and statistical analysis flaws make the results of all studies cited difficult to interpret. We cannot conclude a difference in efficacy or safety among any of the extended release methylphenidate products, or between the immediate release and extended release amphetamine salts, Adderall vs. Adderall XR.[21-28] All but one study cited in Appendix A have serious methodologic flaws. Most of the data presented is analyzed with inappropriate statistics, parametric tests such as t-tests and ANOVAs when the data sets are non-normally distributed, which is inappropriate and results is a type 1 error. One could argue that the data will almost always be non-normally distributed because these tests are truly not continuous data, but in fact nominal or ordinal data, since they are scores that measure ADHD symptoms (e.g., CGI (Teacher and Parents); SKAMP).

Although a recently conducted meta-analysis demonstrates a small statistically significant advantage of Adderall versus methylphenidate for ADHD treatment, these studies included in the analysis were conducted with the immediate release products, and there are concerns regarding selection bias, internal, and external validity.[26] Other studies cited in the AAP Clinical Practice Guidelines did not detect an efficacy difference between Adderall and methylphenidate when dosed equipotently.[2]

The Swanson study was unavailable for review in that it has yet to be peer reviewed and published (Pediatrics, in press); similarly the Data on File at Celltech Pharmaceuticals is also unpublished. However, the Swanson study may be subject to the same limitations as seen with the Lopez study[22], since they were both conducted at the laboratory school utilizing the SKAMP scale. Once peer reviewed and published, a more critical evaluation will be possible.

The pharmacokinetic differences between the extended-release stimulant products reviewed have not demonstrated differences in efficacy.[21-28] Primarily, the advantage of once daily dosage forms is the avoidance of dosing medication during school hours, since both methylphenidate and mixed amphetamine salts are class II controlled substances, and drug diversion as well as school policies and procedures remain paramount issues. As mentioned earlier, administration of medications during school hours, especially C-II medications, is difficult since the medication must be administered by a school nurse, and it must be kept is a safe place to prevent misbranding, adulteration, and drug diversion. In addition, HIPPA mandates patient confidentiality, and ADHD treatment requires additional patient protection since there is a stigma associated with ADHD and the need for drug therapy, especially as perceived by one's peers. Patient confidentiality must remain paramount, and the avoidance of in-school drug administration eliminates HIPPA issues, drug diversion issues, and the need for administration by a school nurse.

IX.   Conclusions

Once daily formulations increase patient compliance, and eliminate the need for medication dosing in schools. Prescribing immediate release stimulants that require dosing during school is problematic, especially with controlled drugs with an abuse potential. Extended release methylphenidate formulations eliminate the need for additional doses during the school day. Both Ritalin LA and Metadate CD may have a pharmacokinetic advantage since both products exhibit a biphasic distribution resulting in Tmax early and late that correspond to every 4 hour dosing intervals with immediate release methylphenidate, the capsules can be opened and sprinkled on food if desired, and the Tmax (early) is achieved at 1.5 to 2 hours post-dose as opposed to 6 hours with Concerta.

Since the desired therapeutic effect is dose dependent, and the need to control the hyperactivity and inattention components during school hours is paramount for continued academic and social success, Ritalin LA and Metadate CD taken with breakfast have a pharmacokinetic advantage that may or may not translate into a therapeutic advantage. However, Concerta maintains more consistent serum concentrations throughout the majority of waking daylight hours (0 to 14 hours post dose); if control of ADHD symptoms is necessary all day long, Concerta may have an advantage over Metadate CD and Ritalin LA.

Thus, although there are pharmacokinetic differences between the extended release branded products, their PK differences have not demonstrated a clinical advantage over one another in terms of efficacy or adverse effects. Yet, due to the extended release properties of all three long acting methylphenidate products reviewed, once daily dosing eliminates the need for in school dosing, and may improve patient compliance.

Patients that have failed, or are intolerant to methylphenidate may be candidates for therapy with mixed amphetamine salts. Since Adderall's AB rated generic equivalents are available from multi-source manufacturers, and pharmacokinetic profiles are similar for the immediate release Adderall and the extended release Adderall XR product all brand products within the mixed amphetamine salts are comparable to each other and to the generics and OTC products in that class and offer no significant clinical advantage over other alternatives in general use.

The three methylphenidate HCl, extended release products within the Rapid Onset, Long Duration Stimulant Agents for ADHD, AHFS Class 282000 reviewed offers significant clinical advantage in general use over the other brands, generics, and OTC products in the same class but are comparable to each other.

X.   Recommendations

Medicaid should work with manufacturers on cost proposals so that at least one extended release methylphenidate product (brand examples include Concerta, Metadate-CD, Ritalin LA) is selected as a preferred agent.

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Appendix A: Efficacy Clinical Trials with Methylphenidate and Adderall Extended Release Dosage Forms

AUTHOR/ Reference	DESIGN	N	Intervention	PRIMARY OUTCOME	RESULTS	LIMITATIONS
Greenhill[21]	R,DB,PC, Parallel	321	Efficacy of Metadate CD (20-60 mg) vs. placebo	CGI (Teacher)	Decreased CGI from 13.6 to 7.4	Inappropriate statistical analysis; potential type 1 error
Lopez[22]	R, SB, PC, Crossover	36	Efficacy of Ritalin LA 20 mg vs. Concerta 18 mg or 36 mg or placebo	SKAMP Scale	Differing PK profiles translate into differing effects on attention and deportment	Inappropriate statistical analysis; potential type 1 error
Wolraich[23]	R,DB,PC, Parallel	282	Efficacy of Concerta once daily vs. methylphenidate immediate release tid vs, placebo	CGI	Concerta and methylphenidate have similar efficacy	Inappropriate statistical analysis; potential type 1 errors (within group) and type 2 errors (between groups)
Pelham[24]	R, DB, PC, Crossover	68	Efficacy of Concerta vs. methylphenidate immediate release tid vs. placebo	CGI	Concerta and methylphenidate have similar efficacy	Inappropriate statistical analysis; potential type 1 errors (within group) and type 2 errors (between groups)
Pliszka[25]	R, DB, PC, Parallel	58	Efficacy of Concerta vs. methylphenidate immediate release tid vs. placebo	CGI	More responders (per dichotomized CGI score) vs. methylphenidate vs. placebo	Methylphenidate may have been under-dosed in this study. Potential type 1 error
Faraone[26]	Meta-analysis	8 studies	Efficacy of Adderall vs. immediate release methylphenidate	CGI	Adderall slightly greater efficacy vs. immediate release methylphenidate	External validity, selection bias, inconsistency between ADHD symptom score and CGI results
McCracken[27]	R, DB, Crossover	51	Efficacy of Adderall vs. Adderall XR vs. placebo	SKAMP Scale	Adderall and Adderal XR have similar efficacy, and both are better than placebo	Non-validated scale, non-continuous data evaluated with parametric statistics; potential type 1 error
Biederman[28]	MC, R, DB, PC	584	Efficacy of Adderall XR vs. placebo	CGI (Teachers and Parents)	Adderall XR has greater efficacy than placebo; similar efficacy with Adderall	ANCOVA versus placebo; not powered to detect differences between doses; not powered to detect adverse effects
Wilens[8]	Prospective, Observational study	407	Long-term methylphenidate efficacy	CGI (Teachers and parents)	Concerta efficacy from baseline to one-year follow-up were similar	Potential type 2 error, several patients lost to follow-up; inappropriate statistical analysis

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Reviews
Miscellaneous Central Nervous System Agent Indicated for ADHD,
Atomoxetine AHFS Class 28:92

I.   Overview

See "Stimulant" monograph for overview information on Attention Deficit Hyperactivity Disorder (ADHD).

Atomoxetine is a newly approved, non-controlled drug therapy that is indicated for ADHD treatment.[1] There is some evidence to support efficacy for ADHD treatment in both children and adults;[1-4] however, little data exists documenting risks associated with atomoxetine since clinical trials are rarely powered to detect differences in adverse effects.[1,5,6] Post marketing surveillance and phase 4 clinical trials will help elucidate potential risks of long-term atomoxetine drug therapy. This review encompasses all dosage forms and strengths.

Table 1: Dosage Forms

Generic Name	Brand Name Example	Dosage Form
Atomoxetine	Strattera	Capsule

II.   Current Treatment Guidelines and Pharmacology

Atomoxetine has not been incorporated into clinical practice guidelines at the time of this writing. Several clinical practice guidelines exist that outline the treatment of ADHD. Some guidelines are primarily consensus-based documents, (i.e., The Texas Children's Medication Algorithm Project: 2000), whereas others are based on evidence-based medicine and consensus (i.e., The American Academy of Child and Adolescent Psychiatry: 2002, and The American Academy of Pediatrics (AAP) Committee on Quality Improvement: 2001). At least 80% of children will respond to one of the stimulants if they are tried in a systematic way. Children who fail to show positive effects or who experience intolerable side effects on one stimulant medication should be tried on another of the recommended stimulant medications. The reasons for this recommendation include the following:

- Most children who fail to respond to one medication will have a positive response to an alternative stimulant
- Safety and efficacy of stimulants in the treatment of ADHD compared with nonstimulant medications has not been established
- Numerous crossover trials that indicate the efficacy of different stimulants in the same child
- Idiosyncratic responses to medication

Children who fail 2 stimulant medications can be tried on a third type or formulation of stimulant medication for the same reason. When the selected management for a child with ADHD has not met target outcomes, clinicians should evaluate the original diagnosis, use of all appropriate treatments, adherence to the treatment plan, and presence of coexisting conditions (strength of evidence: weak; strength of recommendation: strong). The clinician should periodically provide a systematic follow-up for the child with ADHD. Monitoring should be directed to target outcomes and adverse effects by obtaining specific information from parents, teachers, and the child (strength of evidence: fair; strength of recommendation: strong).

Atomoxetine is a neurologic agent with a structure similar to fluoxetine. It is a selective norepinephrine reuptake inhibitor (SNRI) and the first non-stimulant drug therapy approved for ADHD treatment.[1,7] Not

classified as a controlled substance, atomoxetine clinical trials did not suggest a pattern of response typically seen with drugs with stimulant or euphoriant properties.[1] Selective neuronal norepinephrine reuptake inhibition in the brain causes a corresponding increase in norepinephrine in the prefrontal cortex that increases attention and memory. Over time, a resultant desensitization of beta adrenoreceptors occurs. Thus, efficacy is not seen immediately. Three to eight weeks of therapy may be necessary before full therapeutic effects are seen.[2,3] There is minimal to no activity on serotonin or dopamine receptors.

III.   Indications

Atomoxetine is a neurologic agent approved for the management of ADHD in adults and children six years of age or older.[1]

Contraindications for atomoxetine are in patients with closed angle glaucoma since it is associated with an increased risk for mydriasis. In addition, atomoxetine should not be used in patients taking a monoamine oxidase inhibitor (MAOI), and MAOI treatment should not be initiated within two weeks of atomoxetine discontinuation. It is also contraindicated in those patients known to be hypersensitive to atomoxetine or any of its components.[8,9]

IV.   Pharmacokinetic Parameters

Atomoxetine can be taken with or without food. Patients take one dose per 24 hour period. If a dose is missed, it should be taken as soon as remembered, but the total daily dose should not be exceeded within a 24 hour period.[8,9]

Atomoxetine is primarily metabolized by CYP 2D6. Approximately 10% of Caucasians have a CYP 2D6 polymorphism that will decrease metabolism via CYP 2D6 enzyme, thus resulting in much higher plasma concentrations of the parent compound. Poor metabolizers are expected to have a 10-fold increase in plasma steady state concentrations versus extensive metabolizers. Clinical trials thus far were not designed nor powered to detect differences in adverse effects between poor metabolizers and extensive metabolizers, a concern the FDA mentions several times.[8]

Maximum serum atomoxetine concentrations are achieved within one to two hours post dose if taken on an empty stomach. Food decreases Cmax by 37% and delays Tmax by 3 hours.

Serum half life of the parent compound, atomoxetine, is 5 hours in extensive metabolizers, and 22 hours in poor metabolizers.

Clearance is reduced by 50% in patients with moderate hepatic impairment, and 75% in severe hepatic impairment. No dose adjustments are required for patients with renal disease.

V.   Drug Interactions[8,9,12,13]

Albuterol: Co-administration of atomoxetine caused a potentiation of the increased heart rate and blood pressure seen with either drug alone, and was most notable after initial administration of these two drugs. Cytochrome P450 2D6 inhibitors (e.g. paroxetine, fluoxetine, and quinidine): Co-administration increased atomoxetine steady state plasma concentrations similar to that seen in poor metabolizers. May need to decrease atomoxetine dosage.
Methylphenidate: Notably, combined therapy with methylphenidate and atomoxetine did not increase cardiovascular adverse effects and may be a potential treatment modality for refractory patients.
Protein binding interactions: No significant protein binding drug interactions noted.

VI.   Adverse Effects

In clinical trials, the most common reasons for treatment discontinuation included aggression, irritability, somnolence, and vomiting. The most common adverse effects reported include dyspepsia, nausea, vomiting, fatigue, decreased appetite, dizziness, and mood swings. In addition to those adverse effects seen

in children and adolescents, dry mouth, erectile dysfunction, impotence, and abnormal orgasm were reported in clinical trials in adults. Post-marketing surveillance, long term outcomes analysis, and pharmacoepidemiologic data are necessary to determine the frequency of rare, yet serious adverse effects. One in particular, QT prolongation, is a concern of the FDA since in poor metabolizers, the QT interval may be prolonged by 10 to 20 msec. This is controversial due to the variability of the measurement and the lack of long term data. The FDA has mandated long term safety studies that may determine if this QT prolongation is clinically significant.[8]

Monitoring parameters include: Patients that are poor metabolizers via CYP 2D6 will have elevated atomoxetine serum concentrations and may require a decrease in dosage. Routine liver function tests should be conducted since atomoxetine doses must be decreased by 50 percent in patients with Child-Pugh Class B liver dysfunction, and for patients with Child-Pugh Class C liver dysfunction, initial doses should be reduced to 25% of a normal dose. Patients are evaluated for clinical response using an 18-item Total ADHD Symptom score.[11]

VII.   Dosing and Administration

For children and adolescents weighing less than 70 kg, dosing should be initiated at a total daily dose of 0.5 mg/kg and increased after three days to a dose of 1.2 mg/kg as single or divided doses. The total daily dose in children and adolescents should not exceed 1.4 mg/kg or 100 mg: whichever is less. Whereas, for children and adolescents over 70 kg, atomoxetine should be initiated at a total daily dose of 40 mg per day, and increased after three days to the target daily dose of 80 mg per day as a single daily or divided dose. Regardless of weight, the maximum daily dose is 100 mg. Atomoxetine can be discontinued without taper.[8,9]

VIII.   Comparative Effectiveness

Randomized, placebo controlled studies in children and adults have demonstrated the effectiveness of atomoxetine for the treatment of ADHD versus placebo (see Table 2). Yet, it is not clear if there are efficacy differences between methylphenidate, mixed amphetamine salts, and atomoxetine. One open label, prospective, randomized controlled head-to-head study compared atomoxetine to methylphenidate for the treatment of ADHD.[4] The study did not detect an efficacy difference between atomoxetine and methylphenidate, although it is not clear that the study had the power necessary to detect a difference.[10] This study was poorly designed, small, and had unequal variances between groups. The placebo controlled trials are summarized in Table 2. Overall, these studies are confounded, small, short duration, and low levels of evidence. See the comments section in Table 2 for more specific information. Further clinical trials that are double-blinded, randomized, and powered to detect efficacy differences between methylphenidate, mixed amphetamine salts, atomoxetine, and placebo are needed before any conclusions can be made regarding comparative atomoxetine efficacy. Safety will only be determined by post marketing research. The FDA has mandated phase 4 studies to determine long term safety and efficacy.

Table 2: Atomoxetine Efficacy Trials with ADHD RS as Primary Endpoint

AUTHOR/ YEAR	DESIGN	SAMPLE SIZE (N)	DURATION	COMMENTS
Kratochvil 2002[10]	Open label, head-to-head	228 184atom/ 44meth	10 weeks	66 patients did not complete treatment; confidence intervals contain 0; did not detect difference; potential type 2 error; not clear if methylphenidate group was titrated up to effective dose
Biederman 2002[2]	Pooled subgroup analysis from 2 double blind studies	51 females	9 weeks	Level of evidence of an observational study due to pooled data analysis without statistical corrections. Statistically significant differences seen weeks 3 to 8
Michaelson 2001[3]	Randomized, open-label, placebo control	297	8 weeks	1.2 mg/kg/day was more effective versus placebo. Did not detect a difference between 1.2 and 1.8 mg/kg/day Open label design presents bias; unequal variances between groups; used ANOVA with no correction for confounders.
Spencer 2002[4]	Pooled data from 2 randomized, double blind, placebo controlled trials	291	12 weeks	Poor metabolizers were excluded; non equal variances, ANOVA used without correction for confounders such as other drug therapies. Non normally distributed data, therefore, potential type 1 error with parametric analysis

IX.   Conclusions

Pharmacotherapy decision-making depends on many factors including patient past medical history, comorbidities, other drug therapies, and potential for abuse and diversion. Based upon a lack of evidence to support the safety of atomoxetine long term, and the low level of evidence to support efficacy, the brand version of atomoxetine offers no significant clinical advantage over other alternatives in general use. It may be appropriate for some patients, however. Patients that are refractory to methylphenidate and patients that are refractory to amphetamine salts may be candidates for atomoxetine drug therapy. Patients with a substance abuse history may be appropriate candidates for atomoxetine therapy and can be evaluated on a case by case basis.

X.   Recommendations

No brand of atomoxetine is recommended for preferred status.

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